Lipids, lipid-lowering therapy and diabetes complications

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Received 9 August 2010; received in revised form 30 September 2010; accepted 1st October 2010
Available online 3 December 2010

Abstract

Cardiovascular disease (CVD) remains the primary cause of morbidity and mortality in patients with diabetes. Lipid-lowering therapy (LLT) is often required, and statin drugs are usually the first-line therapy. However, even when LDL-cholesterol values are within the target range, a substantial residual risk persists. Fibrates may help to lower this risk, especially in patients with high triglyceride and low HDL-cholesterol levels, as suggested by the lipid ACCORD trial. Furthermore, they may even have beneficial effects on the development of microvascular complications such as nephropathy and especially retinopathy, as suggested by the results of the FIELD study. Data suggest benefit with fenofibrate on diabetic retinopathy, with significant effects on the requirement for first laser treatment and macular oedema. Fibrates, like statins, may act directly to decrease the progression of diabetic complications through their lipid-lowering effects, but may also go beyond that via pleiotropic effects. Recent data and the possible underlying mechanisms are analyzed in this review.

Keywords: Diabetes; Lipids; Statins; Fenofibrate; Nephropathy; Retinopathy; Review

1. Introduction

The burden of diabetes is mostly due to its chronic complications. Microvascular complications such as retinopathy, nephropathy and neuropathy are best prevented by tight glucose control [1,2]. However, achieving near-normal blood glucose levels is not always possible or desirable in patients with advanced diabetes [3]. Furthermore, HbA1c-lowering sometimes fails to significantly improve cardiovascular outcomes [4]. Thus, other ways of preventing complications need to be identified. Blood pressure control has proved effective for the prevention of both macrovascular and microvascular diabetes complications [5,6], but is not always easy to achieve [7] and may still be insufficient. A multifactorial approach is now encouraged in type 2 diabetes (T2D) patients based on the results...
of the Steno-2 study, which showed a persistent, high, residual risk [8].

The role of dyslipidaemia in diabetes macrovascular complications has long been known [9], and lipid involvement has also been implicated in the development of microvascular diabetes complications [10]. Indeed, the importance of lipids and lipid-lowering therapy (LLT) in the management of microvascular diabetes complications has recently been supported [11] by the results of the fenofibrate intervention and event lowering in diabetes (FIELD) study, a large interventional trial of fenofibrate, despite some disappointing cardiovascular outcomes.

The present mini-review focuses on the potential role of lipids in the pathogenesis of microvascular diabetes complications, and on the ability of LLT to lower the risks of diabetic retinopathy, nephropathy and neuropathy.

2. Glucose control and the prevention of complications

As the incidence of diabetes has been growing worldwide [12], the human and monetary costs of diabetes have also been increasing dramatically, and complications are responsible for most of these costs [13]. Landmark trials such as the Diabetes Control and Complications Trial (DCCT) of type 1 diabetes (T1D) [14] and the United Kingdom Prospective Diabetes Study (UKPDS) of T2D [15] have convincingly shown that tight blood glucose control can effectively prevent the development and/or progression of microvascular diabetes complications. Tight blood glucose control can also help to prevent cardiovascular disease (CVD) in T1D [16] as well as in T2D [17], provided that it is introduced early in the course of the disease, as good blood glucose control has a ‘legacy’ effect [18].

However, normal HbA1c values are rarely achieved and sustained in patients with T1D [19] and, when excess mortality was reported among T2D patients in the intensive-treatment group of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Glycaemia trial [20], doubts arose as to the safety of seeking near-normal HbA1c values in patients with long-standing T2D. As a response to this controversial situation, a joint position statement was published by the American Diabetes Association (ADA), the American College of Cardiology (ACC) and the American Heart Association (AHA) [21], recommending that HbA1c values less than 7.0% should remain the target in most patients with diabetes.

Nevertheless, given these circumstances, other ways of reducing complications should also be investigated. One of these might be to act on lipids. In fact, there is no doubt that lipids are involved in coronary heart disease (CHD), and that a reduction in low-density lipoprotein (LDL) cholesterol is associated with a decrease in major cardiovascular events [22]. There is also evidence of the role of lipids in microvascular complications and the benefit of LLT, including statins as well as fibrates, in the prevention of these complications. Furthermore, fibrates may be helpful for reducing the residual risk following statin therapy [23,24]. This idea was tested in the ACCORD trial, in which 5518 patients with T2D, and mean LDL-cholesterol levels at baseline of around 100 mg/dL, were treated with open-label simvastatin and were also randomly assigned to receive either masked fenofibrate or a placebo [25].

3. Role of lipids in diabetes complications

Lipids are classically associated with CVD, and they are also involved in the development of microvascular diabetes complications as well. In fact, both types of complications may share a common causal mechanism. In unification hypotheses, advanced glycation end-products (AGEs) [26], inflammation processes and oxidative stress [27] may all play important roles, interacting with endothelial cells to modulate a large number of cellular properties [28].

3.1. Lipids and cardiovascular disease

CVD remains the primary cause of mortality in patients with diabetes, and was recently found to be responsible for mortality rates ranging from 30% of all-cause deaths in the Veterans Affairs Diabetes Trial (VADT) [29] to 50% in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial [30]. The UKPDS post-trial study, however, did not separate CVD-related deaths from diabetes-related deaths in general. Yet, although CVD-related morbidity and mortality can be prevented by lowering LDL concentrations [31], there is also strong evidence that this strategy may sometimes fail to prevent new events, suggesting that other cardiovascular risk factors may be involved [32].

In this regard, high-density lipoprotein (HDL)-cholesterol levels have been found to play a major role regardless of gender, age and associated cardiovascular risk factors, including diabetes [33]. Indeed, in the treating to new targets (TNT) trial [34], low HDL levels that remained almost unchanged in the 80-mg atorvastatin treatment group would explain, at least in part, the residual risk (13.8%) in patients with CVD and diabetes.

Recently, the results of the arterial biology for the investigation of the treatment effects of reducing cholesterol 6–HDL and LDL treatment strategies in atherosclerosis (ARBITER 6–HALTS) trial [35] gave further support to the protective role of HDL against CVD. Patients with CVD or similar CVD risk levels, and LDL cholesterol less than 100 mg/dL and HDL cholesterol less than 50 mg/dL (men) or 55 mg/dL (women) receiving statin therapy, were randomized to receive either ezetimibe 10 mg or extended-release niacin (target dose: 2000 mg/day). HDL cholesterol decreased slightly with ezetimibe therapy and increased by 18.4% with niacin ($P<0.001$ for between-group difference). However, LDL-lowering was greater with ezetimibe than with niacin ($P<0.01$). Nevertheless, niacin had greater efficacy over the 14-month study period in decreasing carotid intima–media thickness ($P<0.003$). Furthermore, the incidence of cardiovascular events was lower in the niacin group compared with the ezetimibe group (1 vs 5%, respectively; $P=0.04$). This suggests an important role for HDL in the pathogenesis of CVD.
The management of hypertriglyceridaemia is also an important part of CVD prevention. In the pravastatin or atorvastatin evaluation and infection therapy–thrombolysis in myocardial infarction 22 (PROVE IT–TIMI 22) trial, for each 10-mg/dL decrease in triglycerides, the incidence of major cardiovascular events was lowered by 1.6%, after adjusting for LDL-cholesterol values and other covariates ($P<0.001$) [36]. Furthermore, a recent meta-analysis of trials testing lipid-modifying drugs found a significant association between baseline triglyceride levels and stroke risk (adjusted relative risk [RR]: 1.05 per 10-mg/dL increase; 95% CI: 1.03–1.07) [37]. In the ACCORD trial, the incidence rate of cardiovascular events was 70% higher in patients with high triglyceride and low HDL-cholesterol levels vs those without this profile (17.3 vs 10.1%, respectively) [25].

### 3.2. Lipids and diabetic nephropathy

Chronic kidney disease (CKD) is defined by either a low glomerular filtration rate (GFR) or raised urinary albumin excretion (UAE), and is associated to an increased CVD risk [38]. Cardiac death was independently increased by 10% for each 10-mL/min decrement in estimated GFR [39].

Both experimental and clinical studies have shown the deleterious effects of elevated cholesterol levels on renal injury, and on the initiation and progression of diabetic nephropathy [40]. Total cholesterol was a significant factor in the development of abnormally raised UAE, with an RR of 1.4 (95% CI: 1.1–1.7; $P<0.01$) per mmol of total cholesterol [41]. Serum triglycerides have also proved to be an independent risk factor for the development and progression of nephropathy in patients with T1D [42]. More recently, a protective role of high HDL cholesterol has been suggested, with a significant 12% increase in CKD incidence for every 10-mg/dL decrement in HDL concentration [43].

In fact, the pathophysiology of diabetic nephropathy is complex [44], and involves endothelial dysfunction together with glucose and lipid metabolism products and inflammation processes. These mechanisms may also interact with each other: endothelial dysfunction may be secondary to hyperglycaemia, and the decrease in nitric oxide (NO) production might be related to protein kinase C (PKC) activation, oxidative stress, inflammatory processes and/or increased AGEs [45].

The kidney is the major site of AGE clearance [46]. AGEs exert deleterious effects by inducing cross-linkages of proteins such as collagen to promote vascular rigidity. The interaction of AGEs with receptors for AGE (RAGE) enhances intracellular processes that lead to oxidative stress and cytokine production [47]. RAGE activation contributes to the production of vascular endothelial growth factor (VEGF) by podocytes and the activation of inflammation pathways, resulting in a subsequent rise in UAE [48].

However, renal damage is also highly dependent on advanced lipoperoxidation end products [49], which accumulate in the kidneys, triggering receptor-mediated proinflammatory pathways as in atherogenesis. The glycoxidation process appears to play an important role in the development of renal injury only in the presence of hypercholesterolaemia [50], and a negative correlation between concentrations of IgG antibody against oxidized LDL and the estimated GFR has been described in patients with T1D [51].

### 3.3. Lipids and diabetic retinopathy

The role of lipids in the development of retinopathy was first suggested almost 20 years ago [52]. Later, the DCCT results supported the link between lipid levels and the development of macular oedema or hard exudates [53] that had already been described in the Early Treatment Diabetic Retinopathy Study (ETDRS) [54]. In the DCCT, the severity of retinopathy was positively associated with raised concentrations of triglycerides, and negatively associated with HDL-cholesterol levels. Furthermore—but in men only—retinopathy was also positively associated with LDL cholesterol, apolipoprotein B and small LDL particle concentrations [55].

Diabetic retinopathy is the result of microangiopathy and capillary occlusion [56], which lead to microvascular leakage and breakdown of the blood–retinal barrier. The clinical consequences are retinal haemorrhages, exudates, oedema (including macular oedema), ‘cottonwool’ spots and neovascularization. VEGF apparently plays a key role in the pathogenesis of diabetic retinopathy, as its intravitreous concentrations are associated with angiogenesis in proliferative diabetic retinopathy [57]. Moreover, it appears that VEGF is increased not only in the presence of hyperglycaemia, but also in hyperlipidaemic patients, and that lipid-lowering agents (statins and fibrates) can lower VEGF levels [58,59]. Recently, a substudy of the VADT [60] suggested that antiendothelial cell autoantibodies may also be involved and may be contributing to the need for laser therapy.

The presence of diabetic retinopathy in patients with T1D is associated with a higher all-cause mortality rate and incident CVD [61]: this association may be explained by its link with various cardiovascular risk factors, except for proliferative retinopathy, suggesting that other shared mechanisms may also be involved. This independent association with proliferative retinopathy has also been reported in T2D patients [62].

### 3.4. Lipids and diabetic neuropathy

The relationship between lipid disorders and neuropathy is less well known and has been studied only recently. There is a close tie between CVD and diabetic neuropathy. The EURO-DIAB study [63] was a prospective trial of 1407 patients, with T1D (mean age: 32.7 ± 10.2 years; mean diabetes duration: 14.7 ± 9.3 years) and normal vibration perception threshold (VPTs) at study inclusion, who were followed for 7.3 ± 0.6 years. The incidence of abnormal VPTs was 24% over the study period. The presence of CVD risk factors, including total cholesterol and LDL cholesterol, prospectively predicted the development of large-fibre dysfunction, as measured by VPT. Although CVD was present at baseline, the odds ratio for the development of neuropathy compared with patients with no history of CVD was 2.74 (95% CI: 1.68–4.49; $P<0.001$), after adjusting for HbA1c and duration of diabetes [64].

Severe neuropathy has also been reported in association with hypertriglyceridaemia [65], while an independent association between diabetic neuropathy and low HDL cholesterol or high triglycerides has been recently reported too [66].

Wiggin et al. [67] looked at the mechanisms underlying diabetic neuropathy progression in two randomized placebo-controlled clinical trials. Patients were defined as having progressive neuropathy if they lost greater or equal to 500 fibres/mm² in sural-nerve myelinated fibre density over 52 weeks, and were compared with non-progressing patients who lost less than 100 fibres/mm². The loss of fibre density (25% decrease in the progressing cohort vs no change in the non-progressing cohort; \( P < 0.0001 \)) was significantly associated with baseline triglycerides (\( P < 0.04 \)), thus supporting the proposed role of hypertriglyceridaemia in the progression of diabetic neuropathy.

4. Efficacy of lipid-lowering therapy in the prevention of diabetes complications

Recent French statistics have shown that the proportion of diabetic patients receiving LLT increased from 42.7 to 54.9% between 2000 and 2005. At the same time, the proportion of patients taking statin drugs rose from 23.9 to 40.3% [68], indicating that the number of diabetic patients using LLT with a statin rose from around half of all patients to three out of every four patients.

4.1. Lipid-lowering therapy and cardiovascular disease prevention

The first-line LLT for patients with diabetes is currently statin treatment. A recent meta-analysis of 14 randomized controlled trials, involving a total of 18,686 patients with diabetes, found a significant 21% reduction in major cardiovascular events for every mmol decrement of LDL, which was similar to that observed in subjects without diabetes [69]. This effect was reported in primary as well as in secondary prevention (although the absolute benefit was greater among patients in the latter), and was irrespective of other baseline characteristics, even in patients with baseline LDL values less than 2.6 mmol/L (<100 mg/dL). The CHD rate with statins was 8.3 vs 10.5% in the controls (RR: 0.78, 95% CI: 0.69–0.87) and 7.2 vs 9.6%, respectively, in those without diabetes (RR: 0.77, 95% CI: 0.73–0.81). The reduction appeared during the first year (10%), with a subsequent 20–30% reduction per each successive year in those with or without diabetes. This, however, indicates a high residual risk calling for additional strategies.

One such strategy might be the use of a fibrate as monotherapy or in combination with a statin, shown to be as safe as long as the fibrate is not gemfibrozil [70]. Of the other fibrates, the one most studied by far is fenofibrate.

Fenofibrate reduced the progression of CHD on angiographic data in diabetic patients [71]. Its action is characterized by triglyceride reduction, a moderate LDL-lowering effect and an increase in HDL concentrations [72]. The FIELD study [73] was the largest interventional study to use fenofibrate (or any fibrate) in diabetic patients so far. It involved 9795 T2D patients (2131 in CVD secondary prevention, 7664 in primary prevention), aged 50–75 years, who were not taking a statin at study entry. This randomized controlled trial compared micronized fenofibrate 200 mg and a placebo, and the primary outcome was the cardiac event rate (CHD deaths and non-fatal myocardial infarction [MI]). The reduction in RR was not significant (−11%; \( P = 0.16 \)). However, the secondary endpoint (total cardiovascular events), which was also 11%, was significant (\( P = 0.035 \)) because of the large number of events.

However, these FIELD results raised a few issues, as a significant reduction in cardiovascular events was observed only in patients who had no prior CVD (−19%; \( P = 0.004 \)). This might have been due to the fact that, among patients with prior CVD, 14% of those taking fenofibrate and 23% of those taking the placebo received add-on statin therapy compared with 7 and 16%, respectively, of patients in primary CVD prevention [74]. In any case, this was a major confounding factor that reduced the power of the study.

Another noteworthy finding was the small variation in HDL cholesterol: although an initial 5.1% increase in HDL cholesterol was seen at 4 months in the fenofibrate group, this had fallen to 1.2% by the end of the study, mostly because HDL cholesterol was 0.5% lower in the patients who were started on another LLT during the study. Nevertheless, the difference in HDL cholesterol had also decreased to 2.1% at the study end in the group that did not begin another LLT. The reason for such a ‘fade-away’ effect of fibrate therapy on HDL cholesterol is not clear. However, the Veterans Affairs HDL Intervention Trial (VA-HIT) study had also reported a smaller effect of gemfibrozil on HDL cholesterol in diabetic patients compared with non-diabetics [75]. In that study, gemfibrozil induced a greater reduction of major cardiovascular events in patients with T2D, suggesting that HDL cholesterol is not a major predictor of efficacy in cardiovascular outcomes.

A recent meta-analysis of fibrates for CVD prevention in T2D confirmed that long-term fibrate use significantly reduced the risk of non-fatal MI (RR: 0.79; \( P = 0.006 \)), but had no significant effect on total mortality or other adverse CV outcomes [76]. However, a new analysis of the FIELD study [77] could change the way the results are viewed: when silent MI is included in the analysis, it appears that fenofibrate significantly reduced the risk of clinical or silent MI by 19% (\( P = 0.006 \)) and of nonfatal MI by 24% (\( P = 0.01 \)), whereas the risk of silent MI was not significantly decreased (16%; \( P = 0.16 \)) with the placebo. In addition, in those with silent MI, fenofibrate reduced any subsequent clinical CVD events by 78% (\( P = 0.003 \)).

Nevertheless, it should be noted that, in the FIELD trial, there was a non-significant increase in total mortality with fenofibrate vs placebo (7.3 vs 6.6%, respectively; \( P = 0.18 \)). Also, median plasma homocysteine levels increased by 4% in the fenofibrate group compared with the placebo group, and this could be deleterious in diabetic patients [78]. Fenofibrate was also associated with an increase in pancreatitis (0.8 vs 0.5% with placebo; \( P = 0.031 \)) and in pulmonary embolism (1.1 vs 0.7% with placebo; \( P = 0.022 \)), although the numbers were small. These findings were not confirmed by the ACCORD Lipid trial,
which found no increased risk of pancreatitis, deep vein thrombosis or myopathy in the fenofibrate group [25].

Nevertheless, for these reasons, fenofibrate cannot be considered a first-line LLT in patients with diabetes at this time. However, the residual CVD risk that persists with statin therapy, even when mean LDL values are within the target range, was significantly reduced by statin plus fibrate therapy: such a combination induced a 50% fall in triglycerides and a 22% increase in HDL cholesterol, while LDL cholesterol was decreased by 46% (P < 0.0001 for all) [79]. Furthermore, when compared with low- or moderate-dose statins, fenofibrate combined with low- or moderate-dose statins resulted in more than fivefold higher rates of patients concomitantly achieving optimal levels of LDL cholesterol, non-HDL cholesterol, apolipoprotein B, HDL cholesterol and triglycerides (21.6 vs 4.0% with low doses; 20.8 vs 3.0% with moderate doses) [80].

Such a combination has mostly been promoted for patients with the metabolic syndrome, who may be those to benefit the most from fibrate therapy [81]. Indeed, a post-hoc analysis of FIELD data has confirmed this hypothesis, showing that the biggest effect of fenofibrate in reducing CVD risk was observed in those with marked dyslipidaemia (elevated triglycerides, low HDL cholesterol), with a 27% RR reduction (95% CI: 9–42%; P = 0.005) [82]. This could be due to the fibrate effect on LDL particle size [83], as the metabolic syndrome is characterized by the presence of small LDL particles [84]. In fact, most of the benefits of fenofibrate that are beyond its lipid-lowering effect are mediated by peroxisome proliferator-activated receptor-alpha (PPAR-α) activation, and appear to be independent of its actions on glucose and lipid metabolism [85].

However, the recently published results of the ACCORD Lipid trial [25] do not support the use of fenofibrate with simvastatin in patients with T2D, as it failed to reduce the rate of CVD events, non-fatal MI or non-fatal stroke compared with simvastatin alone. Nevertheless, it should be emphasized that the mean LDL cholesterol was 100.6 ± 30.7 mg/dL at baseline, whereas fenofibrate is mostly active on non-LDL lipids. Accordingly, it should be mentioned that, in patients with triglycerides greater or equal to 204 mg/dL and HDL cholesterol less or equal to 34 mg/dL, there was a strong trend towards a lower cardiac event rate in the statin + fenofibrate group compared with the statin + placebo group (12.37 vs 17.32%, respectively) [25]. This result was confirmed by a recent meta-analysis [86] of five major trials: ACCORD, FIELD, VA-HIT, bezafibrate infarction prevention (BIP) and Helsinki Heart Study (HHS). In these five studies, the effects of fibrate were determined in dyslipidaemic patients according to the same criteria (triglycerides ≥ 204 mg/dL and HDL cholesterol ≤ 34 mg/dL) as well as in patients not fulfilling these criteria. The odds ratio for coronary events was reduced by 35% (95% CI: 22 to 46%) in the subgroups with dyslipidaemia, and by 6% (95% CI: −5 to 16%) non-significantly in the others, indicating that fibrate therapy can reduce CVD events in patients with dyslipidaemia.

Data on cardiovascular event-rate reductions with niacin are limited in patients with diabetes. A post-hoc analysis of men in the coronary drug project with a history of MI showed a similar reduction with niacin in the incidences of 15-year total mortality and 6-year MI whether or not they had the metabolic syndrome [87]. Niacin decreases triglyceride levels and increases HDL-cholesterol levels. Extended-release (ER) niacin therapy was recently shown to restore the endothelial vasoprotective effects of HDL in patients with T2D [88]. This may explain why niacin improves small-artery vasodilatory function and compliance in statin-treated patients with T2D [89].

When combined with a statin, ER niacin induced significant regression of carotid intima–media thickness compared with ezetimibe in 38 patients with T2D (out of 363 patients in the study) [35]. However, ezetimibe might have the potential to reduce arterial stiffness in patients with T2D [90].

4.2. Lipid-lowering therapy and chronic kidney disease

LLT might be able to prevent microvascular complications independent of its action on lipid levels through pleiotropic effects [91,92]. Although tight blood glucose and blood pressure control is undoubtedly the best way to prevent diabetic nephropathy, other complementary options are promising. RAGE blockade is an exciting option [93], but is not yet available, and inhibition of AGE formation by compounds such as aminoguanidine could have deleterious effects such as promotion of LDL oxidation [94]. LLT is a much more exciting and currently available option.

The effect of statins on diabetic nephropathy has been extensively studied. LLT is almost always required in diabetic patients with CKD, as an LDL goal of less or equal to 70 mg/dL has been suggested in such high-risk patients [95]. It has also been established that statins lower lipid values and cardiovascular events in patients with CKD irrespective of the stage of disease, although no effect on all-cause mortality or on primary prevention has yet been shown [96].

The pleiotropic effects of statins include actions on endothelial dysfunction, VEGF and inflammatory pathways [91]. A meta-analysis of 13 studies looking at the effect of LLT on CKD progression showed a lower rate of GFR decline with treatment compared with controls (a difference of 0.156 mL/min/month; P = 0.008). There was also a tendency towards lower UAE in the treatment group, but this was not significant (P = 0.077) [97]. A more recent meta-analysis of the effects of statins on albuminuria [98] showed essentially a non-significant 2% reduction of albuminuria in normoalbuminuric subjects (UAER: < 30 mg/day), and significant decreases reaching 48% in microalbuminuric subjects (UAER: 30–300 mg/day) and 47% in macroproteinuric patients (UAER: > 300 mg/day). However, the effect of statins on renal outcome (evolution of estimated GFR) was not statistically significant in patients with diabetic nephropathy [99].

A beneficial effect of fibrates on the progression of nephropathy was first suggested with gemfibrozil: the increase in UAE was significantly less, with a greater or equal to 20% fall in triglyceride concentrations [100]. A reduction in the progression of UAE stage with fenofibrate was reported during the Diabetes Atherosclerosis Intervention Study (DAIS) [101], although it should be emphasized that the mean UAE did not change significantly. This was confirmed by the results of the FIELD study, which showed a reduced progression of UAE category. At the
time of inclusion in FIELD, 19% of patients had microalbuminuria and 3% had macroproteinuria. Of the patients whose albuminuria did not progress or even regressed, there were 2.6% more patients allocated to fenofibrate than to placebo. However, although this percentage is highly significant ($P=0.002$), it is questionable whether or not it is clinically relevant. A recently published, pre-specified, FIELD substudy [102] of 170 patients (83 in the placebo arm, 87 in the fenofibrate arm) showed no differences in the urinary albumin-to-creatinine ratio and diurnal UAE, whereas nocturnal UAE rates showed minor decreases in both groups. Fenoibrate treatment was also associated with a 2-mmHg reduction in systolic blood pressure in the main FIELD trial.

The ACCORD Lipid trial also showed lower incidences of both microalbuminuria (38.2 vs 41.6%; $P=0.01$) and macroalbuminuria (10.5 vs 12.3%; $P=0.03$) with fenofibrate vs placebo, respectively [25].

However, the potentially deleterious effects of fibrates on renal function in patients with advanced CKD have to be borne in mind: usually, such effects are reversible after fibrate discontinuation, but a few cases of permanently increased creatinine have been reported in patients with renal transplants [103]. In those with normal kidney function, fenofibrate did not reduce creatinine (evaluated by insulin clearance) by greater than 20%. It has been hypothesized that the increase in creatinine could be related to a decrease in creatinine clearance [104].

In the ACCORD Lipid trial, creatinine levels increased from 0.93 to 1.10 mg/dL in the fenofibrate group within the first year, and remained relatively stable thereafter. The study drug was discontinued for 2.4% of the patients in the fenofibrate group vs 1.1% in the placebo group because of decreases in the estimated GFR. However, there was no significant between-group difference in the incidence of both haemodialysis and end-stage renal disease (75 patients in the fenofibrate group vs 77 in the placebo group).

The FIELD substudy [102] reported a 14% increase in cystatin C levels with fenofibrate vs 3.6% with a placebo ($P<0.01$), suggesting an impairment in renal function. There was an increase in plasma creatinine concentration in the fenofibrate group that was not compensated for by an increase in urinary creatinine, resulting in an obvious decrease in creatinine clearance. The authors hypothesized several other possibilities to explain the rise in creatinine levels, including an inhibitory effect of fenofibrate on the excretion of creatinine by the kidneys, and an increase in the flow of creatinine from muscle. However, muscle damage does not appear to have been present, as creatinine phosphokinase levels were lower in the fenofibrate group.

Furthermore, the benefit of fenofibrate on the progression of albuminuria was not supported by this substudy of FIELD, as UAE was decreased in both groups. The decrease in UAE could have been due to the change in systolic and diastolic blood pressure observed with both placebo (−2 and −8 mmHg, respectively) and fenofibrate (−6 and −8 mmHg, respectively), and/or to the intensification of the treatment of hypertension with renin–angiotensin system blockers in both groups.

The effect of fenofibrate on renal function may or may not be relevant in clinical practice, but it should be noted that renal follow-up based on creatinine levels could become difficult in patients with borderline renal function.

There are no data on the effect of niacin on diabetic nephropathy. However, it should be noted that 2.3% of patients receiving niacin might develop hyperglycaemia whether they have diabetes or not, with potentially greater rates in patients with T2D [105]; indeed, in such patients, the worsening of glucose control may be harmful. On the other hand, ezetimibe might have beneficial effects on proteinuria in non-diabetic patients with chronic kidney disease partly via a cholesterol-independent effect [106].

### 4.3. Lipid lowering therapy and retinopathy

LLT, whatever the drugs used, apparently plays a role in the evolution of diabetic retinopathy. A dramatic regression of retinal hard exudates after aggressive treatment of hyperlipidaemia with plasmapheresis was reported in two patients [107]. Indeed, statins exert pleiotropic effects, which can protect against retinopathy that might be mediated by their effects on VEGF-induced signaling pathways and on AGE–RAGE signaling pathways [108,109]. However, further clinical trials are necessary to clarify the underlying mechanisms and clinical implications.

Before the recent publication of the ACCORD Eye study, there were only a few small studies of the effects of statins on diabetic retinopathy. Simvastatin 20 mg was reported to slow the progression of retinopathy in diabetic patients with hypercholesterolaemia [110]. Also, a positive association between lipid values and the presence of hard exudates and macular oedema had been previously described, whereas atorvastatin 10 mg was reported to reduce the severity of hard exudates and macular oedema in patients with T2D and hypercholesterolaemia [111], suggesting a causal relationship.

However, experimental data have suggested a dose-dependent dual effect of statins: while a low dose of simvastatin had beneficial effects on angiogenic repair and reduced ischaemia, a larger dose could be harmful by inhibiting the endothelium repair processes and increasing ischaemia-induced neovascular pathology [112]. Nevertheless, no relationship was found between the use of statins and either the incidence or progression of age-related macular degeneration [113].

PPAR-α agonists are also reported to inhibit the VEGF pathway. This could be one of the reasons behind the results reported in the FIELD study [114]. The need for laser treatment was a pre-specified tertiary endpoint of the main study, and involved 9795 patients. Furthermore, in a substudy of 1012 patients, standardized retinal photographs were taken and analyzed by ETDRS criteria. Results showed that lipid levels did not affect the need for laser therapy. However, the requirement for a first laser treatment was significantly reduced in the fenofibrate group compared with the placebo group (HR: 0.69, 95% CI: 0.56–0.84; $P=0.0002$). In most cases ($n=282$; 61%), the first laser treatment was because of macular oedema, while the reason for the remaining 39% ($n=183$) was proliferative retinopathy with no macular involvement. The primary endpoint of the substudy (two-step progression of the retinopathy grade) showed no differences between the two groups except for patients with preexisting retinopathy ($P=0.004$). However, the status of the
retina at study inclusion was not known for all patients (retinal photographs were not routinely collected), the criteria for laser therapy may have differed across clinical centres and the number of events in the substudy was small, precluding any definite conclusions being drawn [115]. Furthermore, it should be noted that the potential effect of fenofibrate on retinopathy progression was not mediated by any effect on lipids, blood glucose control or blood pressure, thus undermining the hypothesis of a direct fenofibrate effect.

Recently, the ACCORD Eye trial [116] provided further evidence that fenofibrate can slow the progression of diabetic retinopathy. This 4-year substudy of the ACCORD included 2856 patients, who were randomized to intensive treatment for glucose control (target HbA1c < 6.0% or 7.0–7.9%), dyslipidaemia (160 mg of fenofibrate plus simvastatin or placebo plus simvastatin) or systolic blood pressure (< 120 or < 140 mmHg). The primary endpoint was the progression of retinopathy by three or more stages, according to the ETDRS severity scale, or the development of diabetic retinopathy necessitating laser photocoagulation or vitrectomy. The results showed that, while intensive treatment of blood pressure did not affect worsening of diabetic retinopathy, intensive treatment of dyslipidaemia with fenofibrate was highly effective, compared with placebo, in reducing the rate of progression of diabetic retinopathy (6.5 vs 10.2%, respectively; adjusted odds ratio: 0.60, 95% CI: 0.42–0.87; \(P = 0.006\)), and appeared to be as effective as intensive vs standard blood glucose control (7.3 vs 10.4%, respectively; adjusted odds ratio: 0.67, 95% CI: 0.51–0.87; \(P = 0.003\)). This effect was independent of glycaemia. However, it should be noted that there was a difference in triglyceride levels at 1 year between the fenofibrate group (120 mg/dL) and the placebo group (147 mg/dL).

The reasons for such a dramatic effect of fenofibrate on retinopathy remain unclear, but could be related to interactions with simvastatin [117]. On the other hand, the effect of intensive blood glucose control on microvascular endpoints was somewhat disappointing, with no effects on composite microvascular endpoints (of advanced kidney and eye disease with or without neuropathy) [118], but this could have been affected by the premature discontinuation of the study [119].

No specific data are available for potential effects of either niacin or ezetimibe on diabetic retinopathy. However, niacin was shown to produce vasodilatation of retinal arterioles in individuals with age-related macular degeneration [120].

4.4. Lipid lowering therapy and neuropathy

Few data are available on this topic. A statin was recently shown to have possibly beneficial effects on the conduction of the fastest sensory fibres in diabetic rats, independent of blood pressure and lipid changes [121]. A recent prospective Australian study of 1237 patients suggested that fibrate use was associated with a significant 70% reduction \((P = 0.025)\) in the risk of neuropathy. In addition, in a 6-year prospective substudy of 531 subjects, statin and fibrate use each significantly reduced the risk of neuropathy by 35 and 48%, respectively \((P < 0.045)\) [122], although further studies are needed to confirm this exciting finding. Furthermore, a recent post-hoc analysis of the FIELD study showed a significant 47% reduction \((P = 0.027)\) in non-traumatic minor amputations with no known large-vessel disease in patients taking fenofibrate [123]; these amputations were more likely related to lesions secondary to small-vessel disease and/or to neuropathy.

5. Conclusion

The pathogenesis of both CVD and microangiopathy in diabetes is complex. LLT is generally required in diabetic patients mainly when complications are present and in those at high cardiovascular risk. Although evidence-based data support statin drug therapy as the first-line LLT for diabetes, a residual CVD risk persists. PPAR-\(\alpha\) agonists such as fenofibrate may help to lower this residual risk, particularly in patients with atherogenic dyslipidaemia (high triglycerides and low HDL cholesterol) and may, at the same time, play a role in the prevention of microvascular complications as well. This, however, needs to be clarified by further studies.

Disclosure of conflicts of interest

Paul Valensi has given lectures for Solvay and AstraZeneca. Sylvie Picard has given lectures, and worked on the writing of papers and on translations for Solvay and Pfizer.

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