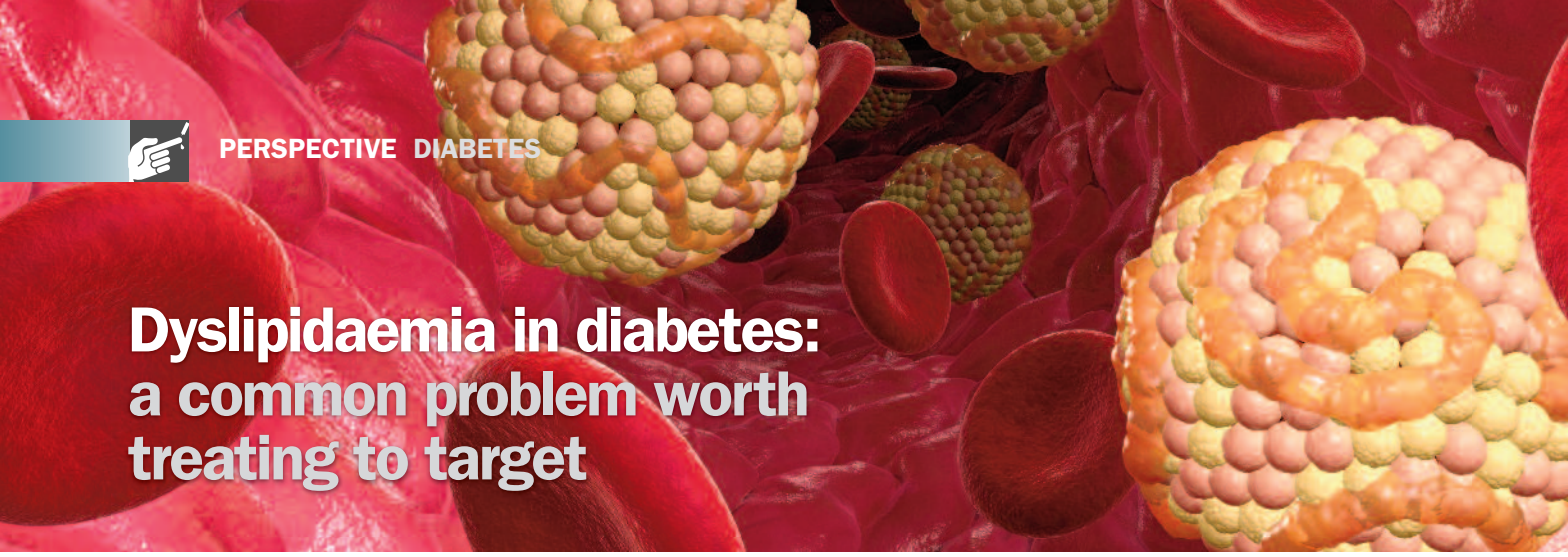



# Dyslipidaemia in diabetes: a common problem worth treating to target

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*Dyslipidaemia is a common problem in people with diabetes. Quantitative and qualitative changes in lipoproteins are thought to contribute to cardiovascular and microvascular complications. Lipid-lowering drugs, such as statins and fibrates, are therefore often required to achieve the recommended lipid levels.*

## Key points

- **Dyslipidaemia is associated with, and predictive of, atherosclerotic events, as well as diabetic retinopathy and nephropathy in both type 1 and type 2 diabetes.**
- **Lipid levels should be checked regularly in people with diabetes and any adverse lifestyle factors or concurrent medical conditions treated.**
- **Lifestyle interventions for improving lipid levels and decreasing cardiovascular risk in people with diabetes include a healthy diet and weight loss (ideally supported by a dietitian), smoking cessation and increased exercise if appropriate.**
- **Use of lipid-lowering drugs, in particular statins (for LDL-cholesterol control) and fibrates (for triglyceride control), are often required to achieve the recommended lipid levels.**
- **Repeated biochemical assessments and counselling are desirable to ensure safe and effective long-term adherence to a lipid control regimen that will reduce the cardiovascular risk in people with diabetes.**

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In 1928, Dr Elliot Joslin stated that 'people with diabetes die of too much fat: too much fat in the diet, too much fat in the body and too much fat in the blood'. Unfortunately, even with the use of modern treatments, this is still the case today, with over 65% of people with diabetes dying of cardiovascular disease (CVD).[1]

Compared with Dr Joslin's time period, our society today has an even higher prevalence of obesity, poor diet and frequent known coexistence of dyslipidaemia and diabetes. Dyslipidaemia is associated with, and predictive of, atherosclerotic events, as well as diabetic retinopathy and nephropathy in both type 1 and type 2 diabetes.[2,3]

Fortunately, we now have access to low-cost assays of the lipid profile and a range of lifestyle and pharmacological treatments that can improve lipid levels and also improve clinical outcomes in people with diabetes.[2-6]

## Dyslipidaemia in diabetes: what and why?

The typical blood lipid profile in people with type 2 diabetes is hypertriglyceridaemia, low HDL-cholesterol (HDL-C) levels and usually relatively normal LDL-cholesterol (LDL-C) levels, which includes many (proatherogenic) small dense LDL particles. In people with type 1 diabetes the lipid profile is relatively normal with good glycaemic control, normal renal function and a healthy weight. Indeed, such people with type 1 diabetes often have lower triglyceride and higher HDL-C levels than their nondiabetic peers.

In spite of this, atherosclerosis is all too common in all types of diabetes, likely contributed to by qualitative changes in lipo-proteins, such as non-enzymatic glycation, oxidation, advanced glycation end-product formation, immune complex formation and altered lipoprotein kinetics and related enzyme activities.[2,3] In type 1 and type 2 diabetes, poor glycaemic control, adiposity, renal impairment and liver dysfunction (such as nonalcoholic fatty liver disease [NAFLD]) elevate levels of triglycerides and small dense LDL particles and lower HDL-C levels.

The guidelines developed by the National Vascular Disease Prevention Alliance, including the National Heart Foundation, Diabetes Australia, Kidney Health Australia and the National Stroke Foundation, were released in May 2012 after approval by the National Health and Medical Research Council.[7] Recommended lipid levels for people with diabetes are shown in the box on page 25. The primary lipid target in most diabetes-related lipid guidelines is LDL-C, given the large evidence base of clinical CVD benefit with LDL-C reduction and the efficacy and safety of statins.

People with diabetes may also have other genetic and/or acquired conditions that induce or aggravate dyslipidaemia (see the box on page 25). These should be sought and, if possible, treated.

## Testing lipid profiles

Dyslipidaemia is usually clinically silent, apart from the end-organ effects that develop over many years but present acutely (such as with a myocardial infarction). Hence, people with diabetes should have their lipid profile tested at least annually, as part of the recommended complication screening, or more often if dyslipidaemia is identified and treated. Rare clinically evident features of severe hypertriglyceridaemia (triglyceride levels more than 20 mmol/L) are a skin rash (eruptive xanthoma), lipaemia retinalis (milky coloured blood vessels on fundoscopy) and acute pancreatitis.[8]

Ideally, lipid levels should be tested after a 12-hour fast (because a nonfasting state elevates triglycerides, which also renders calculated LDL-C levels inaccurate; water is permitted) and not in the setting of an intercurrent or recent illness because these temporarily alter the lipid profile. Nonfasting samples are acceptable but need repeating in the fasted state if the triglyceride level is more than 4 mmol/L.

Total cholesterol, triglyceride and HDL-C levels in serum or plasma are usually measured by enzymatic methods and the LDL-C levels is calculated by the Friedewald equation if fasting triglyceride levels are less than 4 mmol/L (LDL-C = [total cholesterol] – [HDL-C] – [triglyceride level mmol/L/2.2]). Concerns have been raised about the accuracy of the Friedewald equation in people with diabetes because lipid composition may differ from that of nondiabetic people. Some laboratories use a direct LDL-C assay. NonHDL-C, which is used in some guidelines (calculated by [total cholesterol] – [HDL-C]), represents LDL and cholesterol present in very LDL (VLDL) and lipoprotein(a) particles.

Other recommended concurrent tests include $HbA_{1c}$ levels and renal (including urine albumin levels), liver and thyroid function test due to adverse effects of poor glycaemic control, renal and liver disease and hypothyroidism on the lipid profile.

## What is the absolute cardiovascular disease risk?

People with diabetes often have multiple CVD risk factors, such as dyslipidaemia, hypertension, obesity and smoking. Recent recommendations are to treat absolute CVD risk.[5] Absolute CVD risk is the numerical probability of a CVD event occurring within the next five years, expressed as a percentage. Calculators (coloured charts based on the presence of diabetes, sex, blood pressure and total cholesterol/HDL-C ratio) are available at www.cvdcheck.org.au, www.diabetesaustralia.com.au or www.heartfoundation.org.au. The following people with diabetes are automatically at high absolute risk and should be treated aggressively:[7]

- age over 60 years
- prior CVD event
- renal disease (microalbuminuria more than 20 µg/min, urinary albumin:creatinine ratio more than 2.5 mg/mmol for men or more than 3.5 mg/mmol for women, persistent proteinuria or estimated glomerular filtration rate [eGFR] of less than 45 mL/min/1.73 $m^2$)
- marked blood pressure or lipid (total cholesterol more than 7.5 mmol/L) elevation.

The charts are likely to be helpful for guiding therapy in young adults with type 1 or type 2 diabetes without renal or cardiovascular complications. These charts may underestimate the risk for middle aged people with diabetes, Indigenous Australians, and those people with depression at a socioeconomic disadvantage (which are not uncommon associates of diabetes)[7] due to the relatively low representation of these groups in the evidence base from which they were derived.

People at high CVD risk (discussed above) are recommended to be treated simultaneously with interventions for lifestyle and with blood pressure and lipid-lowering drugs regardless of the level of these risk factors. Most patients with diabetes at moderate (10 to 15%) or low (9% or below) absolute CVD risk can be given three to six months to reduce their risk by following lifestyle advice and optimisation of glucose control. Major extensions to the trial of lifestyle changes beyond this time should be avoided as drugs can always be stopped later if major lifestyle changes occur. If risk of CVD remains moderate, or if specific additional risk factors are present, lipid-lowering drugs should be considered.[7]

**Recommended lipid levels in people with diabetes**

**LDL-C level:** less than 2.0 mmol/L
**HDL-C level:** 1.0 mmol/L or more
**NonHDL-C level:** less than 2.5 mmol/L
**Triglycerides (fasting) level:** less than 2.0 mmol/L
**Total cholesterol level:** less than 4.0 mmol/L

**Potential contributing factors to dyslipidaemia in people with diabetes**

- Poor glycaemic control (often associated with elevated free fatty acid levels)
- Adiposity
- Renal disease (e.g. diabetic nephropathy)
- Liver disease (e.g. nonalcoholic fatty liver disease), hypothyroidism (untreated or under-treated)
- Poor diet (e.g. excess alcohol intake, which elevates triglyceride levels, high-fat diet, high-carbohydrate diet)
- Lack of exercise (lowers HDL-C level)
- Smoking (lowers HDL-C level)
- Medications (e.g. thiazides, oral contraceptive pill, corticosteroids, isotretinoin)
- Anorexia nervosa
- Other medical conditions (e.g. myeloma, PCOS)
- Inherited dyslipidaemia (e.g. polygenic hypercholesterolaemia, familial hypercholesterolaemia)

## Management

### Lifestyle interventions

Lifestyle interventions for improving lipid levels and decreasing CVD risk in people with diabetes include a healthy diet and weight loss (ideally supported by a dietitian), smoking cessation and increased exercise if appropriate. Glycaemic control should be improved by lifestyle change or glucose-related drugs if $HbA_{1c}$ levels are suboptimal.[9]

### Lipid-lowering drugs

Lipid-lowering drugs commonly used in people with diabetes are listed in the Table. Each drug affects levels of triglyceride-rich lipoproteins (e.g. VLDL), LDL-C and HDL-C but to different degrees. The major drug class to lower LDL-C levels is the HMG CoA reductase inhibitors (statins) whereas fibrates are the major drug class to lower triglyceride levels.

The primary lipid target in people with diabetes is usually LDL-C; therefore, the first drug class to be considered is a statin. As intensive versus less intensive LDL-C reductions are desirable, the recent more powerful statins (e.g. atorvastatin or rosuvastatin) are usually tried first, but some of the older, less powerful statins (e.g. simvastatin, pravastatin and fluvastatin) may sometimes be useful in patients, for example, who are intolerant of the more powerful statins. The 'rule of six' guides us that doubling a statin dose usually only reduces LDL-C levels by 6%, and is associated with increased risk of adverse side effects.[10] It is our usual practice to start at a low dose (e.g. 10 mg/day in most patients) and to check creatine kinase levels and perform liver function tests before and after statin commencement. Although statin-induced myositis and hepatitis are uncommon, mild-to-moderate creatine kinase elevations (e.g. due to recent exercise) and liver function test abnormalities (e.g. due to NAFLD) are not uncommon and knowing their levels before lipid drug commencement can be helpful in discerning their cause.

If the LDL-C goal (less than 2.0 mmol/L) has not been met or a statin is not well tolerated then ezetimibe, bile acid resins or nicotinic acid should be considered.[7] Of particular relevance to diabetic patients with end-stage renal disease is the recently reported Study of Heart and Renal Protection (SHARP), which demonstrated that simvastatin plus ezetimibe reduced CVD events by 17% relative to placebo.[11] Side effects such as gastrointestinal upset (for resins) and flushing, hepatotoxicity and worsening glycaemia (for nicotinic acid) can be limiting.

In patients with less severe hypertriglyceridaemia, if statin monotherapy is inadequate in lowering triglyceride levels to target, a fibrate with a dose appropriate to renal function should be added. Fenofibrate is highly preferable to gemfibrozil because of a markedly

**Table. Commonly used lipid-lowering drugs in people with diabetes**

| Lipid-lowering drugs | Range of daily doses | Common side effects | Major lipid responses | Tolerability | Evidence of event reduction in diabetes |
|---|---|---|---|---|---|
| Statins | Atorvastatin 10–80 mg<br>Fluvastatin 20–80 mg<br>Pravastatin 10–80 mg<br>Rosuvastatin 5–40 mg<br>Simvastatin 10–40 mg (or 80 mg*) | Myalgia<br>Myositis<br>Abnormal LFTs | ↓↓↓ LDL-C<br>↓↓ TG<br>↑ HDL-C | +++ | Yes |
| Ezetimibe | 10 mg | GIT upset | ↓↓ LDL-C<br>Mild ↓ TG /↑ HDL-C | ++++ | Yes in CKD combined with simvastatin |
| Fibrates | Fenofibrate 48–145 mg<br>Gemfibrozil 600–1200 mg | Myalgia<br>Myositis | ↓↓↓ TG<br>↑ HDL-C | +++ | Modest for some CVD events (e.g. in dyslipidaemia, for revascularisation)<br>Microvascular benefit† |
| Fish oils | 4–12 g | GIT upset<br>Fishy breath | ↓↓ TG | ++ | No |
| Bile acid resins | 4–20 g | GIT upset | ↓ LDL-C<br>Can ↑ TG | + / – | No |
| Nicotinic acid | 2–3 g | Flushing<br>Abnormal LFTs | ↓↓ LDL-C, Lp(a),<br>↓↓ TG<br>↑↑ HDL-C | – | No |

* FDA (USA) guidelines now recommend that new patients should not be commenced on or titrated to 80 mg simvastatin because of the risk of rhabdomyolysis. Existing patients, free from side effects, can continue the 80 mg dose. † Fenofibrate for microvascular complications is an off-label use.

Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease; GIT = gastrointestinal tract; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; Lp(a) = lipoprotein(a); TG = triglyceride.

lower risk of rhabdomyolysis with concomitant statin therapy.[12] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and The Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid study demonstrated that fenofibrate was associated with a greater CVD event reduction in the subset of type 2 diabetes patients with diabetes and dyslipidaemia (high triglyceride level, low HDL-C level).[13-15] In the FIELD and ACCORD studies, fenofibrate was protective against retinal[16,17] and renal[18-20] damage and in the FIELD study also reduced microvascular-related amputations,[21] but use of fenofibrate for microvascular conditions is currently off label.

If fenofibrate is contraindicated, not tolerated or inadequate in lowering triglyceride levels then high-dose fish oils (4 to 12 g/day) or nicotinic acid (2 to 3 g/day) can be added. Fish oils do not usually increase HDL-C levels to the same extent as fibrates or nicotinic acid. Fish oils usually lower triglyceride levels in a dose-dependent manner, with gastrointestinal upset, fishy breath and cost sometimes being limiting factors to tolerability.[7] In the recent Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial, low-dose (1 g/day) prescription fish oil tablets did not reduce CVD events in people with diabetes or prediabetes.[22]

In people with diabetes and moderate or severe hypertriglyceridaemia (with triglyceride levels of 10 mmol/L or more) the lipid-lowering drug of choice is a fibrate, so as to reduce the associated risk of acute pancreatitis. The addition of a statin may be required subsequently to also lower LDL-C levels.

If patients with diabetes cannot achieve lipid goals or are intolerant of the drugs used, specialist advice from a physician interested in lipids should be sought.

### Adherence

Regular checking of lipid levels, up to monthly during drug dosage titration and three- to 12-monthly thereafter, is appropriate in patients with diabetes who are taking lipid-lowering drugs. In patients with diabetes who are not taking lipid-lowering drugs, an annual lipid check is wise, or more often if glycaemic control, diet, weight or renal, liver or thyroid functions deteriorates. As dyslipidaemia itself is usually silent, and often people with diabetes are taking many tablets, potentially with side effects or concerns stemming from media reports, re-education and ongoing (long-term) support are needed to continue an effective lipid control regimen.

## Conclusion

Abnormal lipid problems are very common in people with diabetes, in particular in those with type 2 diabetes. Both quantitative and qualitative changes in lipoproteins are thought to contribute to CVD and microvascular complications. Lifestyle factors and other medical conditions may aggravate dyslipidaemia.

Lipid levels should be checked regularly in people with diabetes and any adverse lifestyle factors or concurrent medical conditions treated. Lipid-lowering drugs, in particular statins (for LDL-C

control) and fibrates (for triglyceride control), are often required to achieve the recommended lipid levels. Repeated biochemical assessments and counselling are desirable to ensure safe and effective long-term adherence to a lipid control regimen that will reduce the cardiovascular risk in people with diabetes. **ET**

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