Guidelines for the management of dyslipidaemia in patients with diabetes mellitus

Quick reference guide

More than 60% of type 2 diabetic subjects in the Eastern Mediterranean Region have some degree of dyslipidaemia. More than 40% of type 2 diabetic individuals have hypercholesterolemia and a further 23% have hypertriglyceridaemia and/or a low level of HDL cholesterol. In contrast, <25% of non-diabetic subjects are hyperlipidaemic. In addition to being the most common lipid abnormality in type 2 diabetes mellitus, hypertriglyceridaemia is also a feature of impaired glucose tolerance and impaired fasting glucose. The purpose of this quick reference guide is to offer proper information and guidance to primary health care physicians, specialists and consultants, and also to policy-makers. They do not attempt to make rigid clinical decisions for physicians and patients. Each clinician must decide, with their patients, the best approach for managing dyslipidaemia in diabetes.

World Health Organization
Regional Office for the Eastern Mediterranean

Characteristics of diabetic dyslipidaemia

- Diabetic dyslipidaemia is characterized by:
  - elevated triglycerides
  - low high density lipoprotein (HDL) cholesterol
  - shift in low-density lipoprotein (LDL) particle density towards small, dense LDL (type B)
  - tendency towards postprandial lipaemia.
- Triglycerides are considered to have atherogenic properties.
- HDL is considered a protective lipoprotein because it contributes to reverse cholesterol transport.
- Small, dense LDL is considered more atherogenic than large, buoyant LDL because it is more prone to oxidation and can trigger inflammatory processes.

Classification

- The following tables classify the levels of total, LDL and HDL cholesterol and triglycerides.

LDL cholesterol classification

LDL cholesterol (mmol/L)	LDL cholesterol (mg/dL)	Classification
<2.58	<100	Optimal
2.58–3.33	100–129	Near or above optimal
3.36–4.11	130–159	Borderline high
4.13–4.88	160–189	High
≥4.91	≥190	Very high

Total cholesterol classification

Total cholesterol (mmol/L)	Total cholesterol (mg/dl)	Classification
<5.17	<200	Desirable
5.17–6.18	200–239	Borderline high
≥6.20	≥240	High

HDL cholesterol classification

HDL cholesterol (mmol/L)	HDL cholesterol (mg/dL)	Classification
<1.03	<40	Low
≥1.55	≥60	High

Triglycerides classification

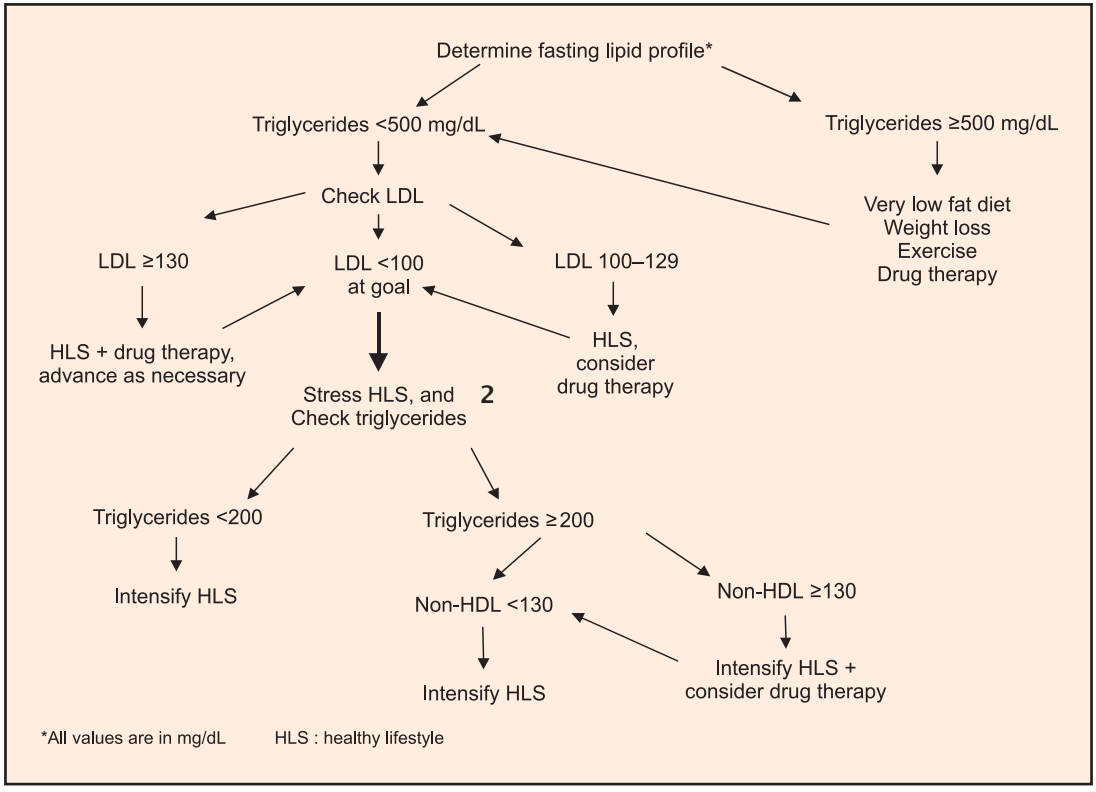
Triglycerides (mmol/L)	Triglycerides (mg/dL)	Classification
<1.69	<150	Optimal
1.69–2.25	150–199	Borderline high
2.26–5.63	200–499	High
≥5.64	≥500	Very high

Screening

- A fasting lipid profile is recommended on a yearly basis for patients with diabetes. The frequency may be decreased to every other year for patients with optimal lipid levels.
- A lipid profile should include measurement of total cholesterol, HDL cholesterol and triglycerides. LDL cholesterol can be calculated, as long as triglycerides are below 400 mg/dL, using the formula LDL cholesterol = total cholesterol – HDL cholesterol – [1/5 x triglycerides]. Otherwise serum LDL cholesterol may need to be measured directly.
- Screening is important in order to identify patients with suboptimal lipid profiles and then institute corrective measures for either primary or secondary prevention.
- If elevated LDL cholesterol or triglycerides are found, clinical and laboratory assessment should be performed in order to rule out secondary causes of dyslipidaemia, such as:
  - hypothyroidism (symptoms, check thyroid-stimulating hormone)
  - obstructive liver disease (liver function tests)
  - chronic renal disease (renal function tests, creatinine clearance, urinalysis)
  - drugs (estrogen, progestins, corticosteroids, thiazides)
  - alcohol (raises triglycerides).

Management goals of diabetic dyslipidaemia

- The primary target of therapy is LDL cholesterol, unless serum triglycerides are ≥500 mg/dL in which case triglyceride-lowering therapy should be started immediately because of the high risk of pancreatitis.
- If or when triglycerides levels are <500 mg/dL, the primary target of treatment is LDL cholesterol and the goal LDL for patients with coronary heart disease or coronary heart disease equivalent (including diabetes) is an LDL cholesterol <100 mg/dL.
- When this is achieved, attention is then shifts to triglycerides. If triglycerides are ≥200 mg/dL, the sum of LDL plus very low density lipid (VLDL) cholesterol, also referred to as non-HDL cholesterol, becomes the secondary target since VLDL, and especially its remnants, are considered atherogenic.
- Non-HDL cholesterol is equal to [total cholesterol – HDL cholesterol], and its goal is 30 mg/dL above the LDL cholesterol goal, i.e. non-HDL goal should be <130 mg/dL in patients with diabetes, assuming a normal VLDL cholesterol to be ≤30 mg/dL.
- For patients with low HDL cholesterol (<40 mg/dL), consider interventions to raise HDL cholesterol level but only after the goals for LDL cholesterol and non-HDL cholesterol (for patients with triglycerides ≥200 mg/dL) have been achieved.



Management of dyslipidaemia

- There is no goal specified for raising HDL in patients with isolated low HDL cholesterol. However, even minimal elevation of HDL should translate into improvement in cardiovascular risk.
- Lipid profiles should be repeated for confirmation when in doubt. The following protocol summarizes the approach for managing dyslipidaemia.

It is recommended to start statin therapy in patients with LDL cholesterol ≥100 mg/dL if they have a history of coronary heart disease.

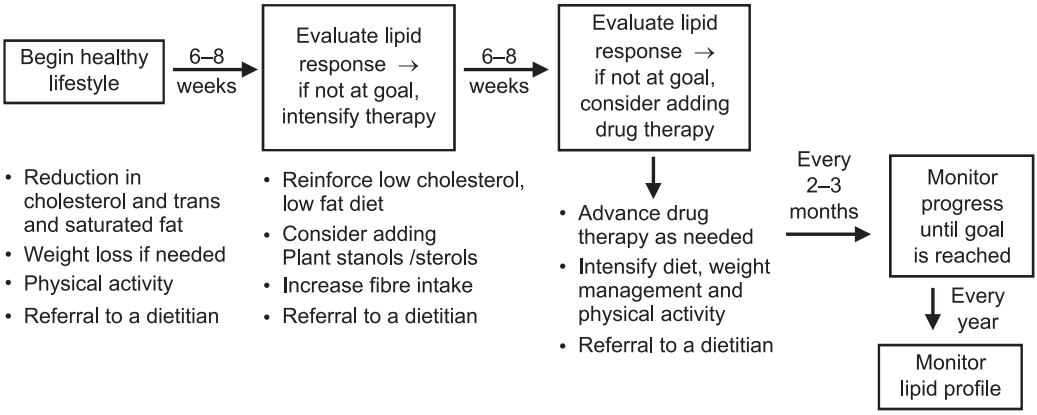
Healthy lifestyle changes

- Dietary interventions, the cornerstone of diabetes management, are also an important means of controlling dyslipidaemia in both diabetic and non-diabetic individuals. Considerable evidence demonstrates the beneficial changes in diabetic dyslipidaemia following dietary alterations, such as changes in nutrient composition.
- Exercise is as an important method of improving diabetes control and reducing the risk of cardiovascular disease. Additional evidence suggests that it has beneficial effects on dyslipidaemia, such as significantly increasing HDL cholesterol levels.
- Healthy lifestyle practices should therefore be emphasized in patients with diabetes. They include:
  - increased physical activity
  - weight reduction for obese patients
  - reduction of food items high in cholesterol, saturated fats and trans-fatty acids
  - increased intake of viscous (soluble) fibres and of plant stanols and sterols which help lower serum cholesterol by limiting its absorption from the gut.

Composition of a healthy diet for patients with diabetes

Nutrient	Recommended intake
Saturated fat + trans-fatty acid	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	30%–35% of total calories
Carbohydrate	45%–55% of total calories
Protein	15%–20% of total calories
Cholesterol	Less than 200 mg/day
Fibre	20–30 g/day
Total calories (energy)	To be determined according to individual needs (whether to maintain or lose weight)

- In patients with elevated triglycerides and low HDL, increasing the intake of unsaturated fat and decreasing carbohydrates may help correct the lipid abnormalities.



Protocol for lipid management

Drug therapy for diabetic dyslipidaemia

- Most patients with diabetes and dyslipidaemia will require drug therapy in order to reach their goals. Different classes of medications are available, with variable effects on LDL, HDL and triglycerides.
- The following is an outline of the characteristics of the commonly used drug classes.

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins)

- Statins are currently considered the drugs of choice for treatment of high LDL cholesterol.
- Some statins, especially the more potent ones, can also lead to significant lowering of triglycerides. They:
  - reduce LDL cholesterol by 18%–55%
  - reduce triglycerides by 7%–30%
  - raise HDL cholesterol by 5%–15%.
- Major side-effects:
  - myopathy or rhabdomyolysis (rare)
  - increase in liver enzymes (usually reversible).
- Contraindications:
  - absolute: liver disease
  - relative: use with certain drugs, due to potential for interaction and increased risk of myopathy.

Statin	Dose range
lovastatin	20–80 mg
pravastatin	20–40 mg
simvastatin	20–80 mg
fluvastatin	20–80 mg
atorvastatin	10–80 mg
rosuvastatin	5–40 mg

- The demonstrated therapeutic benefits of statins are that they:
  - reduce major coronary events
  - reduce CHD mortality
  - reduce coronary procedures (bypass surgery, percutaneous transluminal coronary angioplasty)
  - reduce stroke
  - reduce total mortality.

Bile acid sequestrants

- Bile acid sequestrants are considered second line of therapy for high LDL cholesterol, usually taken in combination with statins.
- They can be used as first-line therapy in patients who are allergic or intolerant of statins.
- Major actions:
  - reduce LDL cholesterol by 15%–30%
  - raise HDL cholesterol by 3%–5%
  - may increase triglycerides.
- Side-effects:
  - gastrointestinal distress/constipation
  - decreased absorption of other drugs when taken concomitantly.
- Contraindications:
  - dysbetalipoproteinemia
  - raised triglycerides (especially >400 mg/dL).

Drug	Dose range
cholestyramine	4–16 g
colestipol	5–20 g
colesevelam	2.6–3.8 g

- Demonstrated therapeutic benefits:
  - reduce major coronary events
  - reduce CHD mortality.

Cholesterol absorption inhibitor

This is a new class of cholesterol lowering medication, aimed at lowering LDL cholesterol. The compound in this class is typically used in combination with a statin when further LDL lowering is desired.

- Major actions:
  - reduce LDL cholesterol by 15%–20%
  - raise HDL cholesterol by 3%–4%
  - no effect on triglycerides.
- Side-effects:
  - minimal

Drug	Dose
Ezetimibe	10 mg

Nicotinic acid

- Despite its side-effects, nicotinic acid may be a useful agent in managing diabetic dyslipidaemia.
- It can lead to significant improvement in triglyceride and HDL cholesterol levels, the two most common abnormalities in patients with diabetes.
- Nicotinic acid may lead to a mild increase in blood glucose. However, this hyperglycaemic effect may be reduced if the drug dosage is kept below 2 g/day.
- A mild increase in HbA_{1c} is to be expected at dosages of over 1500 mg. Such an increase may be remedied by adjusting diabetes therapy.
- Major actions:
  - lowers LDL cholesterol by 5%–25%
  - lowers triglycerides by 20%–50%
  - raises HDL cholesterol by 15%–35%.
- Side-effects:
  - flushing
  - hyperglycaemia
  - hyperuricaemia
  - upper gastrointestinal distress
  - hepatotoxicity.
- Contraindications:
  - liver disease
  - severe gout
  - peptic ulcer disease.

Drug form	Dose range
Immediate release (crystalline)	1.5–3 g
Extended release	1–2 g

- Demonstrated therapeutic benefits:
  - reduces major coronary events
  - possible reduction in total mortality.

Fibric acids

- Fibrates are considered first line therapy for patients with high triglycerides (and adequate LDL).
- The newest agent, fenofibrate, appears to have a lower potential for drug–drug interaction.
- Major actions:
  - lower LDL cholesterol by 5%–20% (with normal triglycerides)
  - may raise LDL cholesterol (with high triglycerides)
  - lower triglycerides by 20%–50%
  - raise HDL cholesterol by 10%–20%.
- Side-effects:
  - dyspepsia
  - gallstones
  - myopathy (especially in patients with renal impairment).
- Contraindications:
  - significant renal or hepatic disease.

Drug	Dose
clofibrate	1000 mg, twice daily
gemfibrozil	600 mg, twice daily
fenofibrate	160 mg, once daily

- Demonstrated therapeutic benefits:
  - reduce progression of coronary lesions
  - reduce major coronary events

Omega-3 fatty acids (fish oils)

- The major role of fish oil is in management of high triglycerides, usually as second- or third-line therapy.

Form	Dose
Fish oil	1–3 g daily

Combination therapy

- A large number of patients with diabetes and dyslipidaemia will require combination therapy in order to achieve their goals.
- Such a situation may occur because one drug is not enough to reach a desirable level for a particular lipoprotein, or because they have a combination of elevated LDL cholesterol and elevated triglycerides, thus requiring dual therapy.

Commonly used combinations of lipid-lowering agents

Combination	Used for	Risk
Statin + bile acid-binding resin	High LDL	Resin may raise triglycerides
Statin + ezetimibe	High LDL	No increased risk
Statin + fibrate	High LDL + high TG	Risk of myositis
Statin + nicotinic acid	High LDL + high TG	
	or High LDL + low HDL	Risk of myositis
Fibrate + nicotinic acid	High TG	
	or High TG + low HDL	Risk of myositis (low)

TG: triglycerides

Glycaemic control and dyslipidaemia

- Improvement in glycaemic control can lead to a less atherogenic lipid profile. Elevated triglycerides tend to improve consistently when glucose levels are lowered, however, the effect of better glucose values tends to be more variable with regard to HDL cholesterol and LDL cholesterol levels.
- Insulin has a consistent effect in lowering triglycerides in poorly controlled patients, while its effects on other lipids tend to be variable. In addition, better glycaemic control is likely to reduce the amount of glycated LDL, and therefore, reduce LDL atherogenicity.
- Always look for secondary causes of dyslipidaemia and treat accordingly.
- Reinforcing a healthy lifestyle (adequate diet, weight loss, exercise) is recommended as a first step for management of dyslipidaemia.

Further reading

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Further information

For further information on diabetes mellitus, consult Khatib OMN (ed.) *Guidelines for the prevention, management and care of diabetes mellitus*, Cairo, World Health Organization Regional Office for the Eastern Mediterranean, 2006 (EMRO Technical Publications Series No. 32) on which this card is based, or contact:

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