ChemBook Issue II
Stories about Lipid Profile Tests

Apo-A

Apo-B

LDL-C

HDL-C
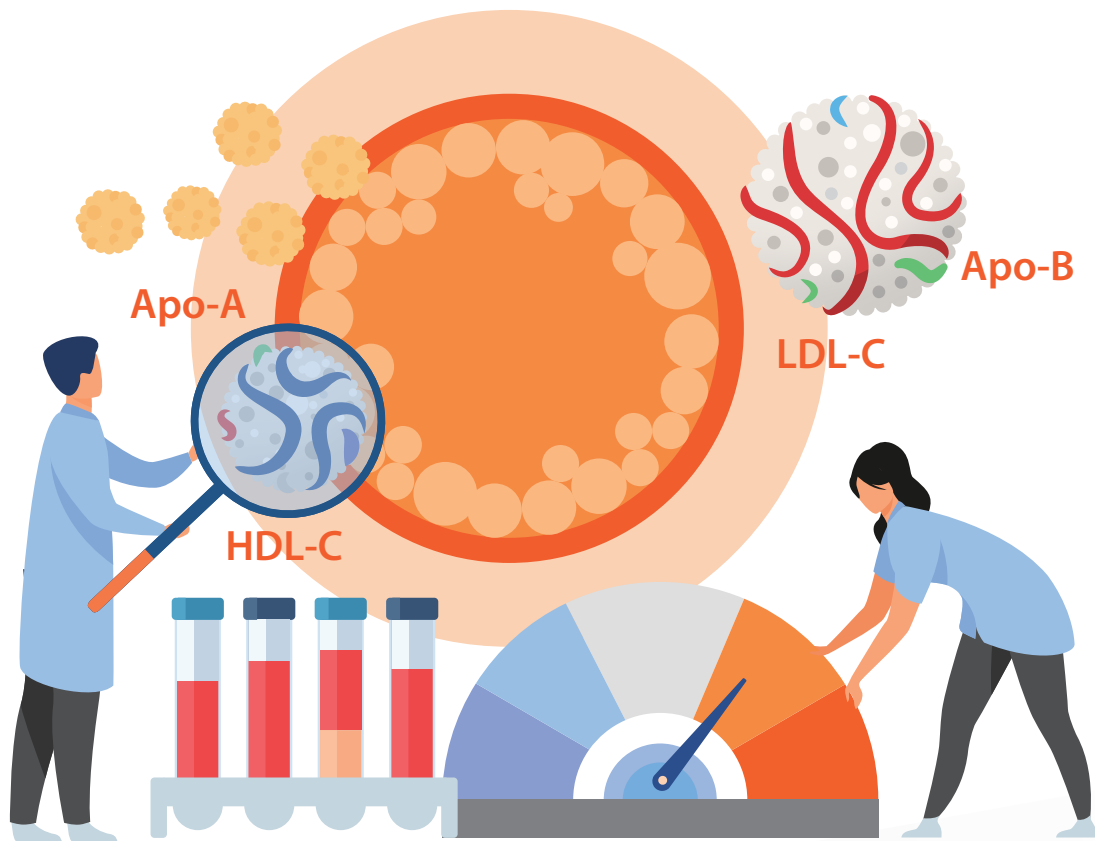
Diabetic Dyslipidemia: Things You Need to Know
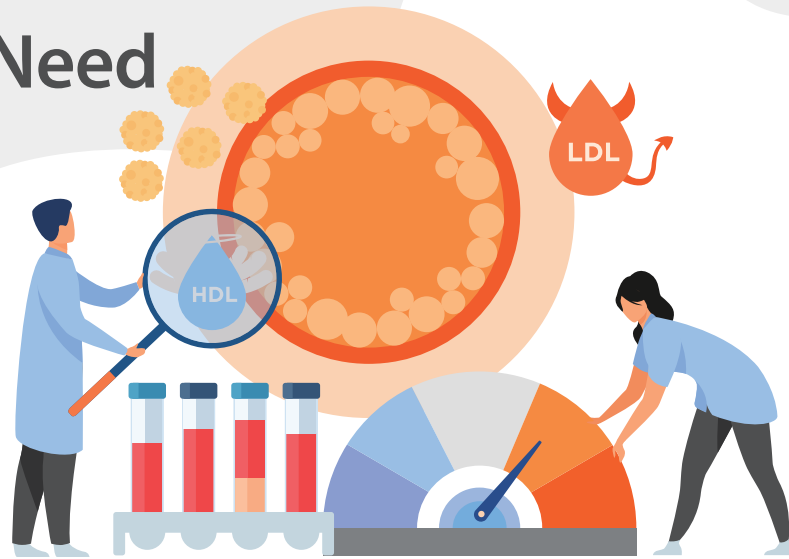
Diabetic dyslipidemia

It is estimated that 415 million people are living with diabetes in the world, which is estimated to be 1 in 11 of the world's adult population. 46% of people with diabetes mellitus are undiagnosed.

Diabetes mellitus is associated with a cluster of interrelated plasma lipid and lipoprotein abnormalities; this common condition is called diabetic dyslipidemia. Diabetic dyslipidemia means that the lipid profile is going in the wrong direction. It is a deadly combination that puts patients at risk for coronary heart disease and atherosclerosis.

Cardiovascular disease could be the most common cause of death in diabetic patients. And the major proportion of CVDs are attributed to the occurrence of atherogenic dyslipidemia.

Diabetic dyslipidemia prevalence

Diabetic dyslipidemia is extremely common in type 2 diabetes (T2DM) affecting around 70% of patients. [1]

A Chinese study shows that the prevalence of dyslipidemia was 39.9%, 46.8%, and 59.3% respectively in Chinese participants with normal glucose, prediabetes, and type 2 diabetes mellitus (T2DM). [2]
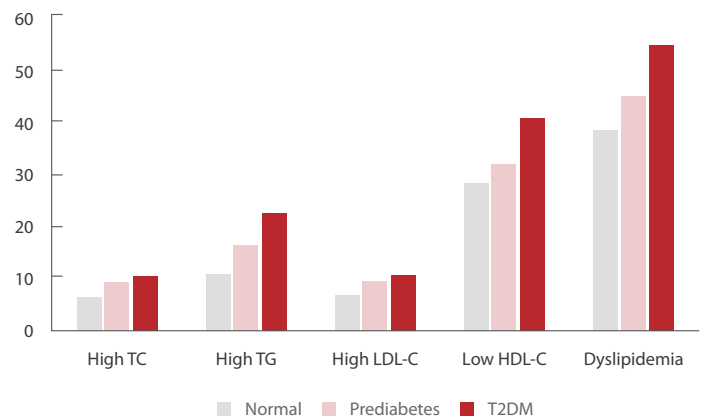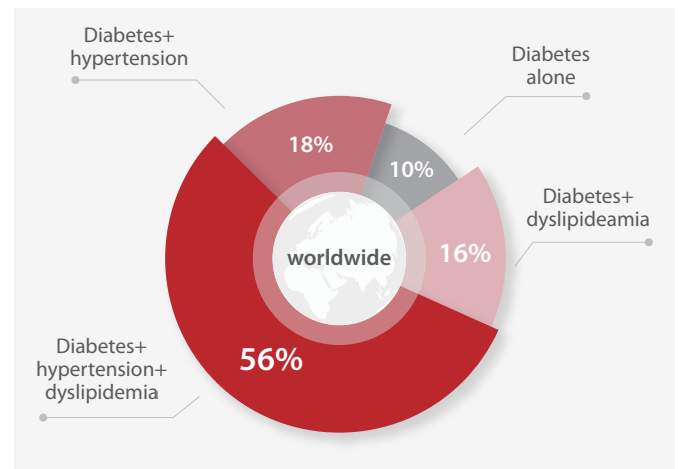

Fig 1. Prevalence of high TC, high TG, high LDL-C, low HDL-C, and dyslipidemia according to diabetic progression stages. [2]

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Causes of dyslipidemia in diabetes

Insulin plays a central role in the regulation of lipid metabolism. Studies show a link between insulin resistance, which is a precursor to type 2 diabetes, and diabetic dyslipidemia, atherosclerosis, and blood vessel disease. Moreover, this dyslipidemia is often found in prediabetics, patients with insulin resistance but normal plasma glucose.
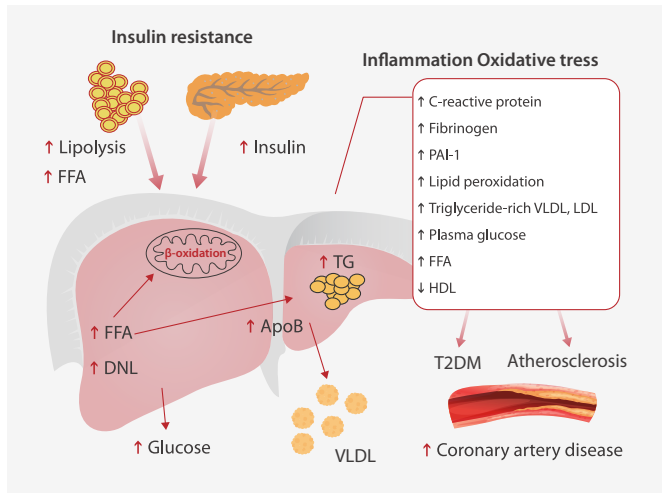

Fig. 2 Link between insulin resistance and metabolic dyslipidemia

Insulin resistance is associated with an increase of free fatty acids (FFAs) flux that contributes to increased TG production that, in turn, stimulate assembly and secretion of VLDL in hepatocytes. Fat accumulation in the liver is associated with oxidative stress and lipid peroxidation. Furthermore, NAFLD subjects have increased secretion of inflammatory markers, plasma glucose, and a decrease in HDL concentration. [3]

In poorly controlled type 1 diabetes and even ketoacidosis, hypertriglyceridemia and reduced HDL commonly occur. [4]

Diabetic dyslipidemia characteristics

Diabetic dyslipidemia comprises a complex group of potentially atherogenic lipid and lipoprotein abnormalities. It is characterized by reduced HDL cholesterol, a predominance of small dense LDL particles, and elevated triglycerides.[5]
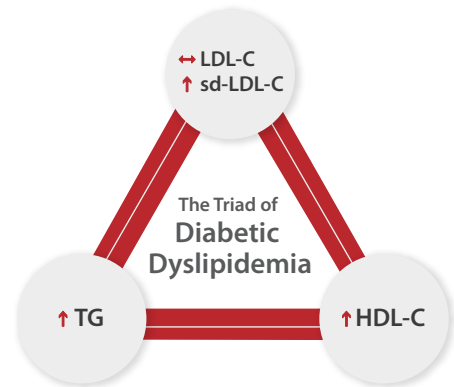

Fig. 3 Diabetic dyslipidemia lipid and lipoprotein abnormalities

Small dense LDL particles are a prominent feature of diabetic dyslipidemia and the number of these atherogenic particles is increased. It has been repeatedly confirmed that the concentration of plasma TG is the most important determinant of the size of LDL. On the other hand, the size of LDL decreases progressively as glucose tolerance worsens, until overt diabetes is achieved. This decrease is greater in women than in men. [6]

Monitoring of the conventional LDL-C may be misleading in diabetic patients; the level of LDLC is not necessarily proportional to the number of lipoprotein particles. It therefore requires specific monitoring for diabetic dyslipidemia patients.

Since each particle of LDL contains a molecule of ApoB-100, the number of small, dense LDL is increased and, similarly, the concentration of ApoB-100 increases in direct relation. Consequently, ApoB concentrations are a marker of the number of atherogenic particles and hypertriglyceridaemia with hyper-ApoB-100 is a well-known feature of diabetic dyslipidemia and other conditions.
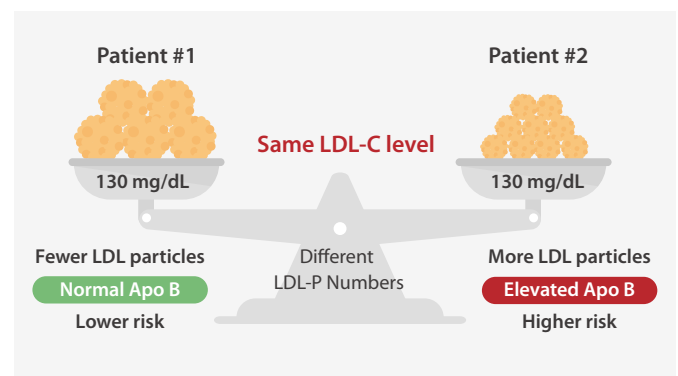

Fig. 4 Same level LDL-C, not necessarily the same number of LDL particles. The number of small, dense LDL particles is increased, the concentration of ApoB is increased, and higher risk of CVD.

Diabetic dyslipidemia Management

Because of frequent changes in glycemic control in patients with diabetes and the effects on levels of LDL, HDL, total cholesterol, and triglyceride, the American Diabetes Association (ADA) recommends that lipid levels should be measured every year in adult patients. If values are at low-risk levels (LDL <100 mg/dl, triglycerides <150 mg/dl, and HDL >50 mg/dl), assessment may be repeated every 2 years. [7]

Lipid goals: various guidelines have proposed different goals for LDL and HDL in diabetics. Each category with different risks should have different lipid test goals. [8]

National Cholesterol Education Program and Adult Treatment Panel II	American Association of Clinical Endocrinologists

• DM and ASCVD
  LDL-C <70 mg/dL
  Non-HDL-C <100 mg/dL
 	
• DM only
  LDL-C <100mg/dL
  Non-HDL -C <130mg/dL
	• Extreme Risk
	  LDL-C <55mg/dL
	
	• Very High Risk
	  LDL-C <70mg/dL
	  Apo-B <80 mg/dL
	
	• High Risk
	  LDL-C <100mg/dL
	  Apo-B <90mg/dL
	
	• Moderate Risk
	  LDL-C <100mg/dL
	  Apo-B <90mg/dL
	
	• Low Risk
	  LDL-C <130mg/dL

Fig.5 Showing recommendations on lipid test goals

Conclusion:

Diabetes is a major public health problem; individuals with diabetes are at high risk for dyslipidemia, cardiovascular disease (CVD), and mortality. To identify and monitor those with lipid disorders, the American Diabetes Association recommends that all adults with diabetes receive a fasting lipid profile test at least annually.

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Clinical Significance of *Lipid Analysis* in CKD Management
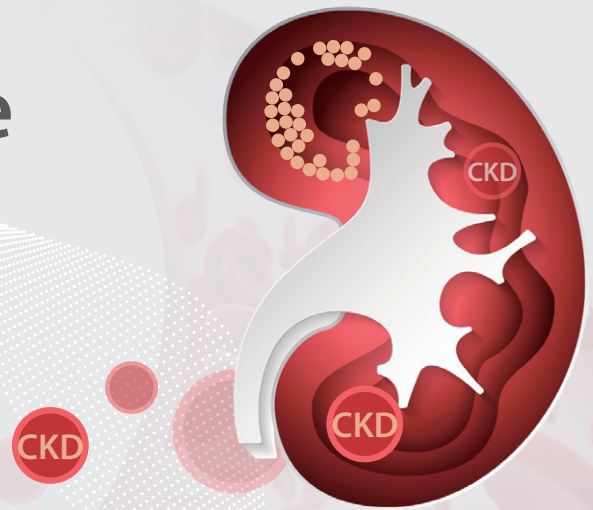
It is widely accepted that laboratory investigation of lipid metabolism is clinically significant for estimating the risk of atherosclerotic cardiovascular disease (ASCVD) and guiding therapeutic decision-making. As recommended by the *2019 ESC/EAS Guidelines for the management of dyslipidaemias*, plasma lipid analysis (e.g. TG, TC, HDL-C, LDL-C, apo B, Lp(a), etc.) and proper treatment are meaningful ways of reducing the risk of ASCVD events. [1]

Recommedations	Classª	Levelᵇ
TC is to be used for the estimation of tatal CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as part of the routine lipid analysis process.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL(>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

Apo=apolipoprotein; CV=cardiovascular; CVD=cardiovascular disease; DM=diabetes mellitus; HDLC=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein(a); SCORE = Systematic Coronary Risk Estimation; TC=total cholesterol; TG=triglyceride.

Figure 1. Guideline recommendations for lipid analysis

Chronic kidney disease (CKD) is one of the world's leading health problems. The estimated prevalence of CKD is 13.4% (11.7%-15.1%), and it is estimated that there are between 4.9 million and 7.1 million patients with end-stage kidney disease needing renal replacement therapy worldwide. [2]
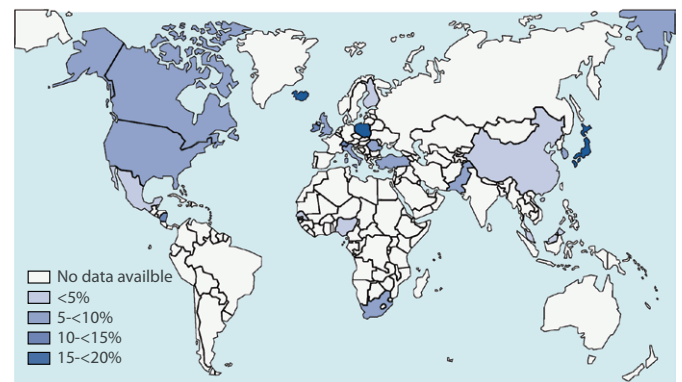

Figure 2. Prevalence of chronic kidney disease [3]

Most patients with CKD are at risk of accelerated cardiovascular disease and death, and many of the cardiovascular comorbidities could be related to dyslipidemia, even though there are significant differences in terms of population, the etiologies of renal damage, the stages of disease progression, and the therapeutic interventions. The level, composition, and quality of plasma lipids could be affected by the altered renal function. The characteristic lipid pattern in patients with CKD stage 3 or higher consists of hypertriglyceridemia, low levels of HDL cholesterol, low levels

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of Apo A1 and variable levels of LDL cholesterol and total cholesterol. Lp(a) levels could also increase in association with CKD. [1, 4]

Free fatty acids

Muscle and adipose tissue

↓ VLDL receptors

↑ Lp(a)
VLDL
↓ LPL
Free fatty acids
IDL
•LDL
↑ Ox-LDL
↑ c-LDL

·Inflammation
·Reactive oxygen species

Liver
•LDLR
•SR-B1

↑ CETP

Cholesteryl ester

↓ HDL

↓ LCAT

HDL precursors

Chylomicron remnants

↓ LPL

Chylomicrons

lecithin-cholesterol acyltransferase

GUT

Macrophages and vascular tissue
↓ ABCA1
↓ ABCG1
↓ ApoA1

→ Endogenous pathway
→ Exogenous pathway
→ Reverse cholesterol transport

Hypertriglyceridemia in CKD results from the delayed catabolism of triglyceride-rich lipoproteins. Apo A1 synthesis is reduced in patients with CKD, and the activation of LCAT by Apo A1 is also decreased. The maturation of HDL precursors is consequently affected. Increased Lp(a) is caused by post-translation modification of lipoproteins related to CKD.

Figure 3. Derangements in lipoprotein metabolism in chronic kidney disease [4]

Consequently, because of the relationship between CKD and dyslipidemia, lipid evaluation is suggested to assist in managing the condition for many patients.

The Kidney Disease: Improving Global Outcomes (KDIGO) organization published its latest guidelines in 2013. As recommended in the clinical practice guidelines, all adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation) should be evaluated with a lipid profile (TG, TC, LDL-C, and HDL-C). Fasting lipid profile tests are suggested, especially for patients with known significant lipid abnormalities. Additionally, for some CKD patients under the age of 50, lipid analysis could help initiate statin therapy and identify any underlying secondary causes of severe hypercholesterolemia and/or hypertriglyceridemia. [5]

For patients who have undergone kidney transplantation, dyslipidemias could be very common, which would put them at high risk of ASCVD and transplant arterial vasculopathy. It is recommended that these patients are assessed for their the risk of developing ASCVD, and a full lipid analysis is helpful. If the lipid profile moves back to a

more normal pattern and such changes are sustained, the risk of ASCVD could be significantly reduced.[6, 7]

Conversely, unlike the LDL-C surveillance involved in managing most patients' treatment, lipid level monitoring is not suggested by the KDIGO work group (2013) in CKD patients with decreased GFR due to the lack of direct evidence. As low GFR is an independent risk factor to ASCVD, strict lipid-lowering therapy would not change medical management or reduce the risk of major cardiovascular events. [5]

However, some trials have revealed that lowering LDL-C is of benefit, as it reduces the cardiovascular risk of CKD patients not requiring dialysis (including kidney transplant recipients), while other guidelines do suggest lipid monitoring to ensure the cholesterol reduction target is met. [4] Therefore, lipid analysis has great potential in the management of CKD patients: in assessing adherence to statin treatment, changes in the renal replacement therapy modality, or concerns about the presence of a new secondary cause of dyslipidemia, and even assessing the 10-year cardiovascular risk in patients aged <50 years and not currently receiving a statin.[5]

To sum up, lipid analysis plays a crucial role in the reduction of ASCVD risks, although lipid testing is quite complicated in patients with CKD, a common medical condition worldwide. All patients with newly identified CKD should undergo lipid analysis, and many of said patients could benefit from medical intervention based on lipid monitoring.

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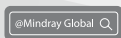
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