DIRECT LDL CHOLESTEROL

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REF No: 02R05-31 3130Tests
REF No: 02R05-21 1532Tests

FOR USE WITH
ARCHITECT

Diagnostic reagent for determination of LDL concentration
Liquid. Dual reagent.Store at +2/+8°C. For In Vitro Diagnostic use. **Do not freeze**.
Products with 02R05-31/02R05-21 Ref Number are produced for Abbott Architect Biochemistry Autoanalyzer Series.

Changes made in the instructions for use are marked as grey.

INTENDED USE

The test is for the quantitative determination of low-density lipoprotein (LDL) in human serum and plasma.

GENERAL INFORMATION

Lipoproteins consist of macromolecular complexes formed by combinations of specific carrier proteins called apolipoproteins and various phospholipids (PL), cholesterol, cholesterol ester and triacylglycerol (TG).[1] Lipoproteins are micelle-like spherical particles with a hydrophobic core containing TG and cholesterol ester and a hydrophilic surface composed of PL and free cholesterol. The size and density of these particles are inversely proportional, so that larger particles are denser than fat, while having a lower percentage of protein.[2] Since cholesterol and cholesterol esters, like TG and PL molecules, are insoluble in water, they are transported by lipoprotein particles in the blood from the tissues where they are synthesized to the tissues where they are stored or used. Different combinations of lipids and proteins form 4 basic lipoprotein particles with different densities ranging from chylomicrons (CMs) to high-density lipoprotein (HDL). These particles can be separated by ultracentrifugation and visualized by electron microscopy.[1] Low-density lipoprotein (LDL) is one of the 4 basic lipoprotein particles.[2] It has a density of 1006-1063 (g/ml) and is composed of cholesterol esters (37%), protein (23%), PL (20%), TG (10%) and free cholesterol (8%). Each lipoprotein class has a specific function determined by the site of synthesis, lipid composition and apolipoprotein content.[2]

Very low density lipoprotein (VLDL) loses TG to form VLDL remnants (also called intermediate density lipoprotein, IDL); further removal of TG from VLDL results in the formation of LDL particles.[1] In addition, apoC and apoE molecules are also lost from the particle structure during the formation of LDL particles and apoB-100 is mainly present in the structure of LDL.[2]

LDLs, which are very rich in cholesterol and cholesteryl esters and contain apoB-100 as the main apolipoprotein, transport cholesterol to extrahepatic tissues with specific plasma membrane receptors that recognize apoB-100.[1]

Elevated LDL is an important causal factor in the development of atherosclerotic cardiovascular disease (ASCVD).[3,4] Therefore, LDL analysis is recommended as the primary lipid analysis method for the screening, diagnosis and management of patients at risk of ASCVD, especially due to dyslipidemia.[5] Furthermore, studies indicate that statin therapy reduces the risk of ASCVD by lowering LDL concentration in the blood.[5-7] In the 2019 guidelines of the European Society of Cardiology and European Atherosclerosis Societies on the management of dyslipidemia, patients' 10-year risk of fatal ASCVD was classified according to the Systematic Coronary Risk Evaluation (SCORE) and treatment was recommended based on risk-stratified target LDL concentrations.[8] Similarly, the American Heart Association (AHA) and the American College of Cardiology (ACC), in their 2018 guidelines on cholesterol management, made lipid-lowering treatment recommendations based on target LDL values determined based on some factors such as ASCVD risk, patient age, and presence of diabetes.[9,10] As a result of high LDL levels, xanthomas may occur in the arcus cornea and achilles tendon, wrist, elbow tendons and metacarpophalangeal joints. Planar or tuberous xanthomas may also be observed in homozygous familial hypercholesterolemia.[11]

In general, in LDL level measurements, it should be kept in mind that lipid levels may vary depending on age and gender, and physiologically, LDL concentrations may increase in the blood during pregnancy and postprandial periods. In addition, blood LDL levels may vary in acute stress conditions such as infection, surgical intervention, myocardial infarction and drug use.[11]

TEST PRINCIPLE

Homogeneous enzymatic colorometric test

The test has a two-step direct measurement method with two main steps involving two reagents:

Phase 1: Polyanion detergent 1 in reagent 1 solubilizes all non-LDL lipoprotein particles except LDL and the released cholesterol esterases are converted into colorless product and consumed by reactions catalyzed by cholesterol esterase and cholesterol oxidase in reagent 1.

$$Cholesterol\ ester \xrightarrow{Cholesterol\ esterase} Cholesterol + Fatty\ acid$$

$$Cholesterol + O_2 \xrightarrow{Cholesterol\ oxidase} Cholestenone + H_2O_2$$

Phase 2: Another detergent in Reagent 2 is specific for LDL and solubilizes LDL, releasing cholesterol esters bound to LDL. At the same time, H_2O_2 formed as a result of the reaction is reduced to water by the enzyme peroxidase, and the colorless chromogen 4-aminoantipyrine is oxidized to quinoneimine, a colored compound. The intensity of the resulting color is measured photometrically at a wavelength of 572 nm (600 nm is chosen as the second wavelength for bichromatic readings) and the obtained absorbance is directly proportional to the cholesterol concentration of LDL.

$$Cholesterol\ ester \xrightarrow{Cholesterol\ esterase} Cholesterol + Fatty\ acid$$

$$Cholesterol + O_2 \xrightarrow{Cholesterol\ oxidase} Cholestenone + H_2O_2$$

$$H_2O_2 + 4 - Aminoantipyrine + TOOS^a \xrightarrow{Peroxidase} Quinoneimine + 4H_2O\ a\ TOOS = N - ethyl - N - (2 - hydroxy - 3 - sulfopropyl) - 3 - methylaniline$$

Note 1: In routine examinations, LDL levels are calculated using the Friedawald formula. The formula is as follows:
LDL-K= TK- [HDL-K + TG/5]

However, this formula should not be used in the presence of CM in the blood, TG ≥ 400 mg/dL and dysbetalipoproteinemia. In addition, direct measurement method is more reliable than calculation in high-risk individuals and thus direct measurement should be preferred.

Note 2: The current reference method for LDL measurement is the so-called "Beta Quantification" method, which combines ultracentrifugation and polyanion precipitation. However, this method is not routinely used because it is time consuming, expensive and requires equipment.[11]

Note 3: It has been reported that the Friedewald equation overestimates the VLDL value and underestimates the LDL value in patients with high TG levels and low LDL levels.[12-14] In a recent study, it has been claimed that if the TG level is 200-400 mg/dL in individuals with low LDL levels (<100 mg/dL) and even if the TG level is below 200 mg/dL in individuals with low LDL levels, the equation calculates erroneously low LDL values.[15,16] In such cases, the application of the "Martin equation" is an alternative method other than direct LDL measurement. In this equation, an adjustable factor value is used to calculate VLDL using the stratified specific median VLDL/TG ratio, instead of the fixed TG/5 ratio in the Friedewald equation.[17] However, it has been reported that the Martin equation cannot calculate LDL with the desired accuracy especially at high TG levels.[12] Another recently developed equation which is said to produce the most accurate LDL result over the equation, especially in patients with low LDL and/or hypertriglyceridemia, is the "Sampson equation".[18] In conclusion, when compared with reference methods, the accuracy rate of LDL calculations based on equations varies depending on some conditions.

REAGENT COMPONENTS

Reagent 1:
Polyanion detergent 1
Cholesterol esterase : ≤ 200.000 U/L
Cholesterol oxidase : ≤ 200.000 U/L
Peroxidase : ≤ 200.000 U/L
4-aminoantipyrine
TOOS

Reagent 2:
Detergent 2
TOOS
Tris Buffer

REAGENT PREPARATION

Reagents are ready for use.

REAGENT STABILITY AND STORAGE

Reagents are stable at +2/+8°C till the expiration date stated on the label which is only for closed vials.

Once opened vials are stable for 30 days at +2/+8°C in optimum conditions. On board stability is strongly related to auto analyzers' cooling specification and carry-over values.

Reagent stability and storage data have been verified by using Clinical and Laboratory Standards Institute (CLSI) EP25-A protocol.[19]

SAMPLE REQUIREMENTS

Serum and plasma can be used and are collected according to the standard procedures. For plasma, sample collection tubes with Li heparin, K2 EDTA and K3 EDTA should be preferred.

LDL activity stability in serum and plasma[31,32]:
7 days +2/+8°C
3 months -20°C
8 months -80°C

Unit Conversion:
mmol/L x 38.61 = mg/dL

Note: Lipid measurements should be performed when the patient has fasted for at least 10-12 hours and is metabolically stable. Venous stasis should be avoided during sample collection.[11]

CALIBRATION AND QUALITY CONTROL

Calibration: The assay requires the use of an Archem HDL-LDL (Arcal Lipid) Calibrator.

HDL-LDL Calibrator (Arcal Lipid)-Lyophilized
Ref.No:01R95-01

Calibration stability is 30 days.Calibration stability depends on the application characteristics and cooling capacity of the autoanalyzer used.

Control: Commercially available control material with established values determined by this method can be used. At least two level controls must be run once in every 24 hours. Each laboratory should determine its own quality control scheme and procedures. If quality control results are not within acceptable limits, calibration is required.

REFERENCE INTERVAL / MEDICAL DECISION LEVELS

For some analytes, it is preferred to use medical decision levels instead of reference ranges. The four basic parameters recommended to be measured as standard for the diagnosis of dyslipidemia are TC, TG, and HDL-C as well as LDL.

According to the ATP III classification, the ideal, normal, borderline high and high values determined for LDL are as follows.[20]

Optimal	: < 100 mg/dL
Normal	: 100 – 129mg/dL
Borderline high	: 130 - 159 mg/dL
High	: > 160 mg/dL

In their 2018 guidelines on cholesterol management, the AHA and ACC specifically highlighted the following levels of medical decision in the application of lipid-lowering therapy, taking into account factors such as ASCVD risk, age, and the presence of diabetes:
LDL ≤70 mg/dL: Target value with combined lipid-lowering drug therapy in patients at very high risk of ASCVD.

LDL ≥160 mg/dL: Resistant LDL blood levels are considered to be one of the risk factors that increase the risk for ASCVD and require the initiation of statin therapy in people without diabetes and with a 10-year risk of developing ASCVD of 5-19.9%.

LDL >190 mg/dL: It is defined as primary severe hypercholesterolemia and requires intensive statin therapy without taking into account the 10-year ASCVD risk, and if the target value of LDL cannot be reduced to ≤100 mg/dL, it is recommended to start combination therapy.[10,21]

The AHA and ACC organizations have also defined normal and abnormal LDL values for childhood in their 2018 guidelines as follows.[21]

Acceptable	: < 110 mg/dL
Borderline	: 110-129 mg/dL
Abnormal	: ≥ 130 mg/dL

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary, determine its own reference range.

Reference interval has been verified by using CLSI EP28-A3c protocol.[22]

PERFORMANCE CHARACTERISTICS

Measuring Interval

According to CLSI EP34-ED1:2018, "Measuring Interval" refers to the interval where the analyte concentration is measured with intended accuracy in terms of medical and laboratory requirements without dilution, concentrating or any kind of pre-treatment that is between the analyte's lower limit of quantitation (LLoQ) and upper limit of quantitation (ULoQ).[23]

The determined analytic measuring interval for LDL is 5-600 mg/dL.

Detection Capability

Limit of Detection (LoD): 4.5 mg/dL

Limit of Quantitation (LoQ): 5 mg/dL

Note: LoQ values are based on Coefficient of Variation Percentage (CV) ≤ 20%.

LoD and LoQ values have been verified by using CLSI EP17-A2:2012 protocol.[24]

Linearity

This method shows measurement linearity up to 600 mg/dL. Autoanaylzer's auto-dilution system can be used if the concentrations have higher values. See device manual for further information.

For the manual dilution procedure, dilute the sample 1:10 using 0.90% isotonic. After this process, multiply the result of the reworked sample by the dilution factor. Do not report the sample result after dilution if it is marked as lower than the linear lower limit. Rerun with a suitable dilution.
Linearity Studies data have been verified by using CLSI EP06-A:2003 protocol.[25]

Precisio

Running system has been developed according to 20x2x2 "The Single Site" protocol. Repeatibility and Within-Laboratory Precision/Within-Device values have been obtained according to the running results.

According to the protocol in use, 2 separate runs per day have been made for 20 days (no obligation for being consecutive days). This protocol has been applied to each low and high samples separately and 80 results have been obtained for each one. Statistically, the results have been obtained using 2-factor Nested-ANOVA model.[26]

Repeatibility (Within Run) and Repeatibility (Day to Day) SD (standard deviation) and CV% values of LDL have been given in the table 1 and 2 respectively.

Table 1. LDL Repeatibility (Within Run) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
42 mg/dL	0.92	2.19	80
109 mg/dL	1.87	1.72	80

Note: This working system has been named "Within-Run Precision" in the previous CLSI - EP05-A2 manual.[27]

Table 2. LDL Repeatibility (Day to Day) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
42 mg/dL	1.25	2.98	80
109 mg/dL	3.52	3.23	80

Note: This working system has been named "Total Precision" in the previous CLSI - EP05-A2 manual.[27]

Interference

Endogenous interferant and analyte concentrations that have been used in the LDL scanning tests has been determined according to "CLSI EP37-ED1:2018" and "CLSI EP07-ED3:2018" manuals.[28,29]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from LDL interference scanning test is appropriate, is determined as ±10%.[30]
In LDL test results, no significant interaction has been observed in the determined endogenous interferant and analyte concentrations or between interferants and analyte.

Interferant and Concentration	LDL Target (mg/dL)	N*	% Observed Recovery
Hemoglobin 900 mg/dL	112	3	93
Bilirubin 22,5 mg/dL	119,4	3	90
Triglycerides 2200 mg/dL	78,4	3	110
Lipemia Index** 702	78,4	3	110

** Total acceptable error rate determined as interference limit and repeatability (within run) pre-detected for the related method were used for the calculations of how many times the control and test samples prepared as a serum pool are going to be run repetitively. In the calculations, the accepted error rate for type 1 (α error) was 5% and for type 2 (β error) was 10% (90% power).*[29]
***No significant interference up to lipemia index of 702. There is poor correlation between the lipemia index (corresponds to turbidity) and triglycerides concentration.*

It should be noted that endogenous interferants, as well as various medicines and metabolites, anticoagulants (e.g. Heparin, EDTA, citrate, oxalate) and preservatives (e.g. sodium floride, iodoacetate, hydrochloride acide) such as additives, materials that may contact with samples during collection and processing (serum separator devices, sample collection containers and contents, catheters, catheter wash solutions, skin disinfectants, hand cleaners and lotions, glass washing detergents, powder gloves), dietary substances known to affect some specific tests (caffeine, beta-carotene, poppy seeds, etc.), or some substances present in a sample that cause foreign proteins (heterophilic antibodies, etc.), autoimmune response (autoantibodies, etc.), or due to malignancy (for example, interference by paraproteins with phosphate testing and indirect ion selective electrode methods) may show some negative effects that will cause various attempts and some misjudgements.[29]

Interferences due to drug treatments or endogenous substances may affect the results.

These performance characteristics have been obtained using an autoanalyzer. Results may vary slightly when using different equipment or manual procedures.

WARNINGS AND PRECAUTIONS

IVD: For in Vitro Diagnostic use only.
Do not use expired reagents.
Reagents with two different lot numbers should not be interchanged.
For professional use.
Follow Good Laboratory Practice (GLP) guidelines.
Contains sodium azide.

CAUTION: Human source samples are processed with this product. All human source samples must be treated as potentially infectious materials and must be handled in accordance with OSHA (Occupational Safety and Health Administration) standards.

Danger

EUH032 :Releases a very toxic gas if contacts with acid.

H317 :May cause allergic skin reaction.

Precaution

P280 :Use protective gloves / clothes / glasses / mask.

P264 :Wash your hands properly after using.

P272 :Contaminated work clothes should not be allowed to be used outside of the workplace.

Intervention

P302+P352 :Wash with plenty of water and soap if it contacts with skin.

P333+P313 :Seek medical help if it irritates your skin or develops rash.

P362+P364 :Remove contaminated clothes and wash properly before using.

Disposal

P501 :Dispose the vials and contents according to the local regulations.

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SYMBOLS

IVD	In Vitro Diagnostic Medical Device
LOT	Lot Number
R1	Reagent 1
R2	Reagent 2
GTIN	Global Trade Item Number
REF	Reference Number
GLP	Good Laboratory Practices
FOR USE WITH	Identifies Products to Be Used Together
PRODUCT OF TURKEY	Product of Turkey
	Manufacturer
	Expiration Date
	Temperature Limits
	Consult Instructions for Use
	Caution
	Number of Tests