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Farooqui Shazia Parveen
Ph.D. Research Scholar, Department of Medicine, National Institute of Unani Medicine, Bangalore, Karnataka, India

Mohd Aleemuddin Quamri
Professor & HoD, Department of Medicine, National Institute of Unani medicine, Bangalore, Bangalore, Karnataka, India

Khaleel Ahmed
Assistant Professor, Department of Ilmul Atfal, LUMCH&RC, Bijapur, Karnataka, India

Arisha Shahid
Ph.D. Research Scholar, Department of Medicine, National Institute of Unani Medicine, Bangalore, Karnataka, India

Corresponding Author:
Mohd Aleemuddin Quamri
Professor & HoD, Department of Medicine, National Institute of Unani medicine, Bangalore, Bangalore, Karnataka, India

Diagnostic criteria of dyslipidemia with lipid fractions & its association with the risk of coronary heart disease: A review

Farooqui Shazia Parveen, Mohd Aleemuddin Quamri, Khaleel Ahmed and Arisha Shahid

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Abstract
Cardiovascular disease is the leading cause of illness and death across world widely. Lipid and lipoprotein metabolism disorder like dyslipidemia patients may prone to develop premature atherosclerosis. Types of dyslipidemia are hypertriglyceridemia, hypercholesterolemia, combined hyperlipidemia, and low levels of high-density lipoprotein cholesterol. Hypercholesterolemia can causes atherosclerosis and hypertriglyceridemia can consequence in pancreatitis. The laboratory findings are beneficial in the analysis and controlling of Dyslipidemia encompass assessment of serum cholesterol, serum triglycerides, serum high-density lipoprotein cholesterol, and serum low-density lipoprotein cholesterol by directly and through calculation. Laboratory investigation which are helpful to eliminate secondary causes of Dyslipidemia are assessment of TSH, Blood sugar levels, liver function test, serum creatinine, and plasma and urine protein level.

Keywords: Lipid profile, fractions, coronary heart diseases

Abbreviations
TSH: Thyroid-Stimulating Hormone
CVD: Cardiovascular disease
CHD: Coronary Heart Disease
NCEP: National Cholesterol Education Program
ATP: Adult Treatment panel

Introduction
CVD is the primary cause of mortality worldwide [1]. The main strategy to reduce its morbidity and mortality comprises the control of cardiovascular disease risk factors, such as dyslipidemia, which has an important modifiable risk factor [2]. Understanding the relationship between lipids and risk of coronary heart disease is an essential for prevention of cardiovascular events [3]. Dyslipidaemia is the most common factor for cardiovascular morbidity and mortality [2]. According to Gupta R *et al.*, Dyslipidaemia is the most important atherosclerotic risk factor [4]. Globally, CVD is the primary cause of mortality and high mortality rate present in low- and middle-income countries [4]. In India, the frequency of CVD has increased dramatically during the last two decades, accounting for 24 percent of all deaths among persons aged 25 to 69 years [5]. CVD now occurs at a younger age in Asian Indian populations than in other populations [6]. Sedentary lifestyles along with urbanisation and nutritional alterations are the most likely causes of a rise in CVD occurrences. Dyslipidemia is a modifiable cardiovascular disease risk factor that has been linked to the pathophysiology of the disease. Asian Indians, on the other hand, have a unique dyslipidemia pattern, with reduced serum HDL cholesterol, high triglyceride levels, and high serum LDL cholesterol [6].

Lipoprotein composition and metabolism
Lipid is insoluble in plasma, so it cannot transported directly through the blood. Lipids are transported by lipoproteins. They are transported in almost all organs and remain in circulation to compensate the energy demands. By density gradient centrifugation of plasma,

different lipid fractions can separated out in chloroform-methanol organic phase as shown in Figure1 [7, 8].

Lipoproteins

Lipoproteins are a group of heterogeneous substances, circulating through the vasculature and existing in a state of dynamic equilibrium between tissues and liver. Internally, a lipoprotein transports triglyceride-fats and cholesterol esters, which are protected from water by the phospholipid monolayer and Apo-proteins. Because of these qualities, it can be dissolved in a salt water-based blood pool. The hydrophilic groups of phospholipids, cholesterol, and apoproteins are directed outward in these lipoprotein particles (Figure 2). Constitution of the major classes of lipoproteins is shown in Table 1 [8].

Although dyslipidemia is often asymptomatic, a screening test is essential for identifying patients who require treatment. A fasting lipoprotein profile should be performed once every 5 years in all individuals aged 20 years or older for risk stratification. Every 4 to 6 years, people with a family history of early CVD and severe dyslipidemia should get a fasting lipid test to confirm their total cholesterol and triglyceride, HDL-C, LDL-C, and non-HDL-C levels. To assess dyslipidemia and the possibility of cardiovascular risk, several lipid fractions and lipoproteins can be measured. High TG, raised small dense LDL-C, and low HDL-C are all indications of hypercholesterolemia, which is linked to atherogenic and diabetes-related dyslipidemia. Patients with such dyslipidemia face a high risk of coronary heart disease (CHD) [8].

According to NCEP- ATP III guidelines, elevated TG is measured as very LDL (VLDL) as marker for atherogenic remnant lipoproteins or non-HDL-C. Furthermore, NCEP ATP III guidelines implemented that non-HDL-C is calculated by subtracting HDL-C from total cholesterol and should be a secondary target if TG is>200 mg/dL. Atherogenic dyslipidemia are interconnected and each component predicts CHD risk [9].

Assessment of lipid profile level

According to the diagnostic procedures, the measurement of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein-cholesterol (HDL-C) levels in the morning after overnight fasting (8-12 hours) to determine LDL-C level using the Friedewald method is the initial step in the laboratory investigation of dyslipidaemias. The lipid profile can be determined using serum. Serum is commonly collected in CLOT- ACTIVATOR tubes, which contain a clot activator and a serum separator gel. Centrifugation at 4,000 rpm for 10 minutes will separate the serum. Triacylglycerol, cholesterol, and HDL-cholesterol are all measured in serum. The Friedewald formula will be used to calculate the VLDL-cholesterol (VLDL) and LDL-cholesterol (LDL). Chemical reagents will be used to measure cholesterol, triglycerides, and HDL-C. When the triglyceride concentration was less than 4.0 mmol/l, LDL-C was estimated using the Friedewald formula [10].

The NCEP-ATP III criteria recommend that assessing total and HDL cholesterol is the first step in diagnosing dyslipidemia. The relationship between LDL cholesterol levels and CHD risk is continuous over a broad range of LDL cholesterol levels from low to high, and HDL cholesterol levels are primarily assessed to determine atherosclerotic risk. Therefore, ATP III adopts the classification of LDL cholesterol levels shown in Table 2; [11].

The Friedewald formula can be used to calculate LDL cholesterol from total cholesterol, total triglycerides, and HDL cholesterol measurements [11].

LDL-Cholesterol (mg/dl) = Total cholesterol (mg/dl)- HDL- Cholesterol (mg/dl) – Triglycerides (mg/dl) / 5

However, if the patient is not fasting or if the triglyceride level exceeds 400 mg/dL (4.52 mmol/L) or if the patient has chylomicronemia, this method is invalid because substantial errors in the LDL-C level may arise. Although direct assessment methods for assessing LDL-C levels have been used in clinical settings, significant difference in accuracy and results obtained between kits have been discovered, particularly in cases with high TG levels [8, 11].

The refrigerator test may be beneficial in determining the existence of high VLDL or chylomicron levels in patients with high fasting triglyceride levels. A turbid infranate indicates an increased VLDL level in a plasma sample kept in the refrigerator for 18 hours; a creamy layer on top suggests the presence of chylomicrons [8, 11].

Lipid fractions

VLDL (Very low-density lipoprotein-Cholesterol), LDL (Low-density lipoprotein-Cholesterol), and HDL (High-density lipoprotein-Cholesterol) are the three lipoproteins that carry cholesterol in fasting serum. The sum of these three components is total cholesterol [12].

Total Cholesterol (mg/dl) = HDL-C (mg/dl) + VLDL-C (mg/dl) + LDL-C (mg/dl)

The total cholesterol, total triglycerides, and the amount of cholesterol found in the HDL fraction, which is easily precipitated from serum, are all measured in most clinical laboratories. The majority of triglyceride is found in VLDL particles, which have five times the amount of triglyceride by weight as cholesterol. Divide the triglyceride by 5 to calculate the amount of cholesterol found in the VLDL fraction [13].

VLDL (mg/dl) = Triglyceride (mg/dl) / 5

Because triglyceride levels are used as a proxy for VLDL, this formula only works with fasting samples and triglyceride levels of 400 mg/dL. LDL and VLDL cholesterol levels can be determined after ultracentrifugation or by direct chemical measurement at higher triglyceride levels [13]. Total cholesterol levels remain relatively stable over time; however, measurements of HDL and, in particular, triglycerides can differ significantly due to laboratory analytic error and biologic variability in a patient's lipid level. As a result, the LDL should always be estimated as the mean of at least two measurement techniques; if the two estimates differ by more than 10%, a third lipid profile is obtained. The LDL is estimated as follows:

LDL-Cholesterol (Mg/dl) = Total Cholesterol (Mg/dl) - HDL-Cholesterol (Mg/dl) – (Triglyceride (mg/dl)/ 5)

When using SI units, the formula becomes:

LDL-Cholesterol (mmol/L) = Total Cholesterol (mmol/L) - HDL-Cholesterol (mmol/L) – (Triglyceride (mmol/L) / 2.2)

Understanding the relationships between the different lipid fractions is more accurate than total cholesterol in determining a patient's lipid-related coronary danger. Two

people with the same total cholesterol level of 275 mg/dL could have very different lipid profiles. One person may have an HDL cholesterol of 110 mg/dL and a triglyceride of 150 mg/dL, resulting in an estimated LDL cholesterol of 135 mg/dL; the other person may have an HDL cholesterol of 25 mg/dL, a triglyceride of 200 mg/dL, and an LDL cholesterol of 210 mg/dL. If no other factors differed, the second would have a more than tenfold higher CHD risk than the first. Many women with apparently high total cholesterol levels have favourable lipid profiles due to high HDL cholesterol levels. As a result, determining the lipid fractions prior to beginning therapy is critical [14].

Some authorities consider the total-to-HDL cholesterol ratio to be an indicator of lipid-related coronary risk: the lower the ratio, the better. (In the preceding example, the first person would have a ratio of 275 110 = 2.5, whereas the second would have a much lower ratio of 275 25 = 11.) While ratios can be useful predictors within patient populations, they can also obscure important information in individual patients. (A total cholesterol of 300 mg/dL and an HDL of 60 mg/dL yield the same 5 ratio as total cholesterol of 150 mg/dL and an HDL of 30 mg/dL.) Furthermore, the total cholesterol-to-HDL cholesterol ratio will exaggerate the significance of variations in HDL measurements. Cholesterol levels in Western populations are around 20% higher than in Asian populations, with about 5% of adults exceeding 300 mg/dL. LDL cholesterol levels above 200 mg/dL are found in around 10% of adults. In people, who are otherwise healthy, total and LDL cholesterol levels appear to increase with age.

When the serum triglyceride level in a pancreatitis patient is excluded, there are declines in acute illness, and lipid studies in such patients are of little benefit. Cholesterol levels do not remain constant over time, particularly during childhood, adolescence, and early adulthood. Thus, children and young adults with relatively high cholesterol levels may have lower levels later in life, whereas those with low cholesterol levels may have higher levels.

Risk determinants for dyslipidemia [11]

a) Cigarette smoking, b) Hypertension (BP 140/90 mmHg or on antihypertensive medication) c) Low HDL cholesterol (<40 mg/dL), d) Family history of premature CHD (CHD in male first degree relative<55 years; CHD in female first degree relative<65 years), e) Age (men 45 years; women 55 years).

ATP III categorises risk into three categories based on these risk determinants, which alter the goals and modalities of LDL-lowering therapy. It aids in the description of these categories and displays the corresponding LDL-cholesterol targets (Table 03). CHD and CHD risk equivalents are included in the highest risk category. The latter have a risk of major coronary events equal to that of established CHD, i.e., more than 20% every ten years (i.e., more than 20 of 100 such individuals will develop CHD or have a recurrent CHD event within 10 years).

CHD risk equivalents include the following:

1) Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
2) Diabetes Mellitus;
3) Multiple risk factors with a 10-year risk of CHD of more than 20%.

Risk assessment method: counting major risk factors and estimating 10-year CHD risk

The following procedure [15] is used to identify high-risk individuals who do not have clinical manifestations of atherosclerotic disease such as CHD or other clinical forms of atherosclerotic disease.

1) The number of risk factors should be determined.
2) For individuals with multiple (2+) risk factors, a 10-year risk assessment using Framingham scoring is performed to identify individuals whose short-term (10-year) risk warrants consideration of intensive treatment.

Estimating the 10-year CHD risk adds a step beyond risk factor counting to the risk assessment process, but it is essential as it allows for better targeting of intensive therapy to those who will benefit from it [16]. When a 0-1 risk factor is present, Framingham scoring is not required because 10-year risk rarely reaches levels that require serious action; however, a very high LDL level in such a person may prompt consideration of pharmacological therapy to lower long-term risk [17]. Framingham scoring considers age, total cholesterol, HDL cholesterol, blood pressure, and cigarette smoking as risk factors. Total cholesterol is recommended for 10-year risk assessment as it has a larger and more robust Framingham database than LDL cholesterol, and though LDL cholesterol is the primary goal of therapy [18],[19]. Framingham scoring divides people with various risk factors into three groups: those with a 10-year risk of CHD of more than 20%, those with a risk of 10-20%, and those with a risk of 10%. It should be noted that this two-step sequence can be reversed and produce essentially the same results [20]. The major risk factors are used for the initial risk assessment in ATP III to define the core risk status. Other risk modifiers should only be considered for changing the therapeutic strategy after the basic risk status has been determined [21].

Table 1: Compositions of Major Lipoproteins [8]

Class	Protein (%)	Cholesterol (%)	Phospholipid (%)	Triacylglycerol (%)
High density lipoprotein	33	30	29	8
Low density lipoprotein	25	50	21	4
Intermediate density lipoprotein	18	29	22	31
Low density lipoprotein	10	22	18	50
Chylomicrons	<2	8	7	84

Table 2: LDL, total, and HDL cholesterol (mg/dL), serum triglyceride, and cholesterol/HDL ratio (ATP III classification) [11]

LDL cholesterol	
Optimal	<100 mg/dl
Near optimal/above optimal	100-129 mg/dl
Borderline high	130-159mg/dl

High	160-189 mg/dl
Very high	≥ 190 mg/dl
Total Cholesterol	
Desirable	< 200 mg/dl
Borderline high	200-239 mg/dl
High	≥ 240 mg/dl
HDL cholesterol	
Low	< 40 mg/dl
High	≥ 60 mg/dl
Serum Triglyceride	
Normal	<150 mg/Dl
Borderline-high	150–199 mg/dL
High	200–499 mg/dL
Very high	≥500 mg/dL
Cholesterol/ HDL Ratio	
Normal	< 4.5
Risk to develop Cardiovascular events	>4.5

Table 3: Three categories of risk that modify LDL cholesterol goals [11]

Risk Category	LDL Goal (mg/dL)
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors*	<130
Zero to one risk factor	<160

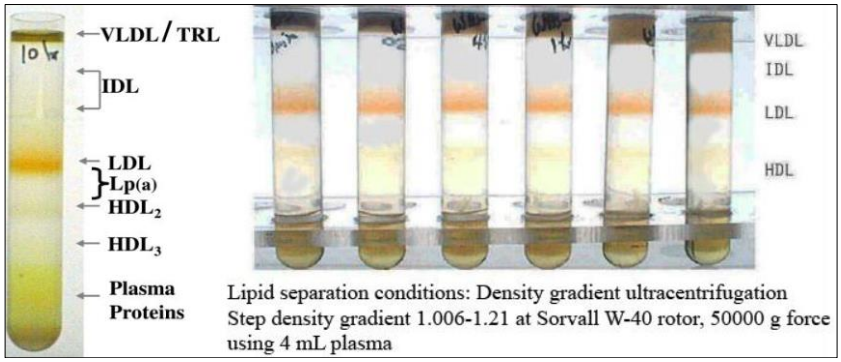

Fig 1: Lipid separation condition: Density gradient centrifugation

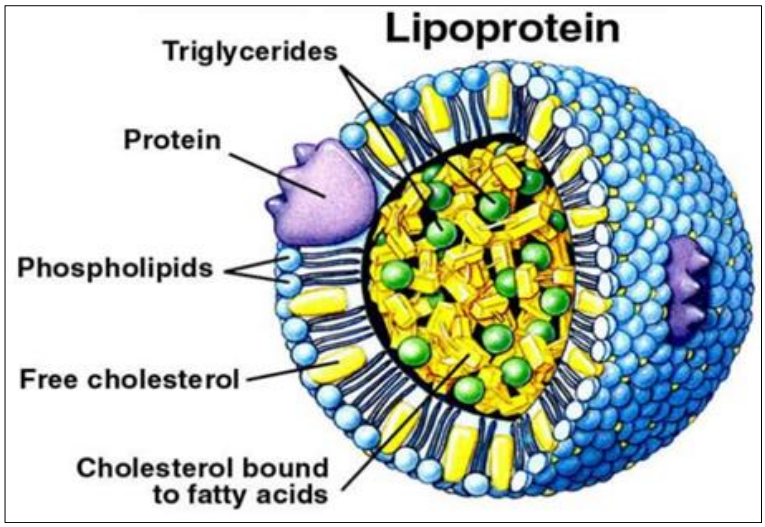

Fig 2: Diagrammatic representation of lipoprotein and cholesterol molecule

Conclusion

Individually, CHD continues to take a toll on the number of lives lost and the quality of life for cardiac event survivors. Unless the disease is controlled and/or prevented, the economic burden on individuals and society will continue to rise. In light of this, it is concluded that patients with CHD have a different lipid profile, with higher levels of TGs, total cholesterol, VLDL and LDL and lower levels of serum HDL; this difference may play a role in the pathophysiology observed in patients with CHD.

Conflict of Interest
Not available

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Not available

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