
# Values of TG/HDL and LDL/HDL ratios in atherosclerotic disease


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ABSTRACT

An abnormal ratio of triglycerides to HDL (TG/HDL) indicates an atherogenic lipid profile and a risk for the development of coronary disease. Dyslipidemia is one of the independent risk factors for atherosclerotic disease. We determined whether the LDL/HDL ratio is better than LDL or HDL alone in predicting the severity of atherosclerosis. The study was performed on 100 patients with myocardial ischemia who underwent coronary angiography between October 2023 and Feb. 2024 in the heart center in Najaf City. Our result showed that only TG/HDL-c and HDL-c were useful for detecting extensive atherosclerosis disease, with the former more strongly associated with the disease. Although some lipid variables were associated with the extent of atherosclerosis disease, the ratio of triglycerides to HDL-cholesterol showed the strongest association with the extent Higher LDL/HDL ratio was seen in CAHD patients than in controls (LDL/HDL ratio was significantly associated with the severity of coronary vascular stenosis.



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| **Keywords:** | Values , atherosclerotic disease , HDL |


## Introduction

**1-1-** Definition

Arteriosclerosis is known as Arteriosclerotic Vascular Disease or ASVD, it is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol. It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells and promoted by low density (especially small particle) lipoproteins (plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL), is commonly referred to as a hardening or furring of the arteries. It is caused by the formation of multiple plaques within the arteries (1).

The atheromatous plaque is divided into three distinct components:

1. The atheroma ("lump of wax", from Athera, wax in Greek,), which is the nodular accumulation of a soft, flaky, yellowish material at the center of large plaques, composed of macrophages nearest the lumen of the artery

2. Underlying areas of cholesterol crystals

3. Calcification at the outer base of older/more advanced lesions

## 1-2- Lipid and Lipoprotein Profile Markers

Atherogenic dyslipidaemia is characterized by a high level of LDL-c (low-density lipoprotein cholesterol), accompanied by an increase in TG (triglycerides), an increased number of sdLDL (small dense LDL), low HDL-c (high-density lipoprotein cholesterol),and postprandial hyperlipidaemia [2–4]. Atherogenic dyslipidaemia is considered to beresponsible for the development and progression of the atherosclerotic process. The panel of atherogenic risk markers consists of non-HDL-cholesterol and apolipoprotein B-100 measurements, together with LDL-c, which measures the free and esterified cholesterol in LDL [5] Along with the determination of lipoprotein concentration in the blood, it is important to take into consideration that the lipoprotein classes encompass particles with distinct protein and lipid profiles. In addition to the traditional risk factors, such as those established by Framingham study, new biomarkers emerged [3].

### 1.2.1. Low-Density Lipoprotein (LDL)

Many studies have demonstrated that high levels of LDL represent a risk factor for cardiovascular diseases associated with atherosclerosis [6]. The structure of LDL particles is represented by a hydrophobic core (built up by cholesterol esters and triglycerides) surrounded by amphipathic lipids (free cholesterol and phospholipids). Apolipoprotein B-100 is also located on the surface of the particle, with an estimated 90% of the total Apo B-100 in circulation belonging to LDL alone. LDL is formed from the catabolism of VLDL (very low-density lipoproteins), which includes the formation of IDL (intermediate-density lipoprotein). VLDL and IDL also contain Apo B-100 [7]. The role of LDLs is to transport the hydrophobic cholesterol in the aqueous medium of blood plasma [4,5,8]. Afterwards, the LDL particles are transferred into the cells by receptor-mediated endocytosis, thus providing the necessary cholesterol [9]. LDL is considered the most important factor involved in the process of atherosclerosis. When oxidative stress is present, an excessive amount of reactive oxygen species is generated, and LDL particles are oxidized (ox-LDL). It is considered that ox-LDL, rather than native LDL has atherogenic traits [8]. Additionally, a high concentration of ox-LDL in atherosclerotic plaques makes them more prone to rupture [6]. Morphological modifications that occur at the level of endothelial cells lead to an increased permeability for LDL particles. The accumulation of ox-LDL in the subendothelial space is one of the initial events in the formation of atherosclerotic plaque [8]. Since the link between LDL and atherosclerosis was highly studied, beginning in the 1950s [5], the determination of LDL-c has become a routine in most laboratories. The Friedewald formula is used to calculate LDL-c,

using the concentrations of total cholesterol (TC), HDL-cholesterol (HDL-c), and triglycerides: LDL-c = TC − HDL-c − TG/5. The results are expressed in mg/dL [5,10]. Factors such as high levels of triglycerides (>4.5 mmol/L) or low levels of LDL-cc (<1.8 mmol/L) in the sample lead to an underestimation of LDL-c [4]. Direct assays of LDL-c are also available, although these may lead to inaccurate results in the case of the structural modification of lipoprotein particles [5]. For research purposes, the determination of ox-LDL was performed using autoantibodies, murine monoclonal antibodies, or malondialdehyde -LDL, but the assays did not prove to be robust [11,12]. The quantity of cholesterol in LDL particles may vary, but there is just one ApoB protein per atherogenic particle (VLDL, IDL, LDL). ApoB represents a better estimation of the number of LDL particles in circulation, compared to LDL-cholesterol [13]

### 1.2.2. High-Density Lipoprotein Lipidome

The concept that high levels of HDL-c represent a protective factor against atherosclerosis is being challenged. Therapeutical interventions that led to an increased level of HDL did not reduce the cardiovascular risk. Attention is now drawn towards the ability of HDL to promote the cholesterol efflux from macrophages, which seems to be inversely correlated with atherosclerosis risk [17,18] and also towards other functions of HDL, including involvement in the process of inflammation, antioxidative properties, and antidiabetic effects. Since HDL particle components are very heterogenous in size, surface charge, and composition, new therapeutic strategies focus on improving the function of HDL, rather than increasing the level of HDL-cholesterol [19]

An emerging technology, proton nuclear magnetic resonance (1H-NMR), is used in lipidomic assessments. The technique provides a valuable insight on the identification and quantification of lipid components [20]. A study investigated the lipid profile (HDL and non-HDL) using the proton NMR-based lipidomic analysis, in 99 patients with coronary heart disease. The alteration in lipid profile, exposed by this technique, allowed a distinction between the stages (mild, moderate, and severe) of coronary stenosis [21]. The same technique was used in another study to evaluate the same two profiles in patients with triple vessel disease, pathology defined as “a ≥50% diameter luminal narrowing in all 3 major epicardial vessel systems“. Patients with coronary heart disease had lower levels of phospholipids and polyunsaturated fatty acids, and higher levels of saturated fatty acids, cholesterol, and triglycerides [22].Kostara et al. investigated the HDL composition in healthy patients compared to patients with a recent diagnosis of type 2 diabetes mellitus and patients with acute coronary syndrome. They reported a progressive alteration of HDL composition within these groups, reflected in high levels of triglycerides, lysophosphatidylcholine, and saturated fatty acids, accompanied by low cholesterol, phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, plasmalogens, and polyunsaturated fatty acids [20]. Another study confirmed that coronary heart disease and type 2 diabetes mellitus patients present an alteration of composition and function of HDL [23]. For patients with diabetes, an increase in small triglyceride-rich particles was reported in the HDL composition, in detriment of large and very large particles, an alteration that could be due to an increased CETP (cholesteryl ester transfer protein) activity. The situation is reversed in patients with coronary heart disease, with an increase in large HDL particles. Although determination of HDL-c is used extensively in medical practice, new studies suggest that it should be replaced by biomarkers that could better evaluate the correlation of HDL-c level with the atherosclerosis process [5]. Monocyte-to-high-density lipoprotein ratio (MHR), a novel marker of inflammation, is considered to have prognostic value regarding cardiovascular diseases and mortality [24].

An increased ratio was associated with a poor outcome at three months after an acute ischemic stroke in patients with atherosclerosis [25]. Another determination that can estimate the atherogenic risk is represented by the calculation of the so-called “non-HDL cholesterol”: non-HDL-c = TC − HDL-c. The advantage of this determination is that it takes into consideration the cholesterol in the remnant

lipoproteins (remnant chylomicrons, remnant VLDL) and in lipoprotein (a) (Lp (a)). The use of non-HDL-c was proposed for patients with high levels of triglycerides that would not allow an accurate estimation of LDL-c, calculated with Friedewald equation. Several studies showed that non-HDL-c is as good as LDL-c in evaluating the risk for cardiovascular diseases (or even better in the presence of hypertriglyceridaemia) [4] and, moreover, non-HDL-c is used for the estimation of 10-year fatal and non-fatal cardiovascular disease risk in SCORE2 («Systematic COronary Risk Evaluation», age 40–69 years) and SCORE2-OP («Older Persons», age 70–89 years) algorithms, developed by the European Society of Cardiology [26]. ApoA1 is the major protein in HDL particles. The ratio ApoB/ApoA1 is considered an indicator of the balance between pro- and antiatherogenic lipoproteins, with a high ratio being associated with a high risk [7]. A study conducted by Florwall et al. showed a strong association between ApoA1 and cardiovascular morbidity and mortality in a group of Swedish men, 77 years of age, who were selected from the participants in the Uppsala Longitudinal Study of Adult Men (ULSAM) [27]. Patients treated with statins are considered to be at risk for atherosclerotic cardiovascular disease, even in the presence of optimal levels of LDL cholesterol. Statins inhibit the synthesis of cholesterol, but triglyceride-rich lipoproteins also have atherogenic potential. A recent study with a set of participants treated with statins, selected from the Copenhagen

### 1.2.3. Triglycerides (TG)

Triglycerides travel in plasma as a component of chylomicrons (CM), very low-density lipoprotein (VLDL) and their remnant particles. Chylomicrons contain apolipoprotein ApoB-48 and triglycerides from dietary fat, while VLDL particles contain Apo B-100 and triglycerides synthesized in the liver. Lipoprotein lipase, located on the vascular endothelial surface, degrades the circulating triglycerides [29]. Fatty acids released from triglycerides lead to dysfunction of the vascular endothelium, one of the first traits of the atherosclerotic process and increased oxidative stress [30,31]. Apo CIII, an apolipoprotein mostly associated with VLDL, may inhibit the activity of lipoprotein lipase and may decrease the uptake of particles which contain triglycerides by the tissues. A recent study demonstrated that apolipoprotein CIII is associated with the risk of cardiovascular events in patients with coronary artery disease [32]. Hypertriglyceridaemia (HTG), defined as a serum triglycerides level >150 mg/dl, is strongly associated with cardiovascular disease. A study conducted on a population of Korean adults, aged 30–49 years, showed that hypertriglyceridaemia is an independent risk factor for cardiovascular events [33], while another study, on the Italian population, confirmed the association between hypertriglyceridaemia and an increased risk of atherosclerotic cardiovascular events [34]. A recent study, which selected patients from two observational cohort studies, demonstrated the usefulness of measuring the average triglycerides levels over time instead of taking into consideration one single measurement or the maximal value. Additionally, the study reported an association between TG and cardiovascular risk even at a level of TG between 100 and 150 mg/dL [35]

### 1.3.Signs and symptoms

Atherosclerosis is a systemic disease that usually affects all major blood vessels of the body. Based on this, the symptoms are also different. Mainly heart, brain, legs suffer. Symptoms are specific, but atherosclerosis is not so obvious that it can be diagnosed without additional methods.[36]

Its symptoms depend on which organ suffers more from lack of blood circulation. In any form of atherosclerosis, two symptomatic periods are distinguished. In the pre-clinical period, the process is just beginning, so a specific manifestation of the disease is not observed. The main problems related to the blood supply and functioning of the organs begin when more than half of the arterial space is closed.[37]

Pain in the heart is manifested in 75% of cases. Atherosclerosis affects the coronary vessels and impairs the delivery of oxygen and nutrients to the myocardium. The heart is one of the organs that is very

sensitive to changes in the intensity of nutrition. Only the brain surpasses it in this respect. Symptoms of the disease develop immediately, it is important to correctly interpret the patient's feelings. Violation of normal blood circulation in the heart is manifested by angina pectoris syndrome. [38]

Symptoms occur periodically and include:

1.Pain in the chest area. There is a pressing, persistent, increasing or burning sensation (these are typical symptoms of an ischemic process). The painspreads to the shoulder blade, left shoulder, wrist and fingers (along the entire length of the circulatory system);

2.A feeling of pressure in the chest (as if a heavy load was placed on the chest);

3. Painful sensations during breathing (also during exhalation);

4.Respiratory disorders.

5.Angina is paroxysmal (with attacks) as a feature of atherosclerosis. During attacks, there is instability in the level of blood pressure.

6.In rare cases, atherosclerosis of the coronary vessels is manifested by the following symptoms:

7.Pain in the left lower jaw, ear, neck;.

8.Pain in the shoulders;

9.Feeling of weakness in the arms and legs;

10.A feeling of chills, sweating and varaja (skin tingling);

11.Tachycardia or bradycardia (heart rhythm disorder);

12.Vomiting and nausea;

13.Confusion or short-term loss of consciousness

14. The intensity and periodicity of symptoms directly depends on the level of tension of the body (stress, overeating, abuse of psychoactive substances, etc.).[39][40]

### 1.4. Risk factors

Atherosclerosis starts in childhood, and is accelerated in some individuals. A cluster of clinical and biochemical factors constitute the risk profile for many of them, perhaps most important being metabolic insulin resistance syndrome. Insulin resistance and its components for children and adolescents, especially obesity and dyslipidemia, are generators of hypertension, glucose intolerance and complications of atherosclerosis in adulthood. Some individuals are genetically predisposed, particularly those with the family history of such disorders. For many subjects, there is ‘tracking’ of metabolic and lifestyle factors from early age to adulthood. Several new risk factors of atherosclerosis (e.g. level of lipoprotein (a), procoagulant state, hyperhomocysteinemia, low birth weight and adverse in-utero environment, and possibly inflammatory markers) are current and potentially future areas of research concerning children and young individuals. Other risk factors for atherosclerosis and its thrombotic complications include hypertension, cigarette smoking and diabetes mellitus. Increasing evidence also points to a role of the immune system, as emerging risk factors include inflammation and clonal haematopoiesis. Studies of the cell and molecular biology of atherogenesis have provided considerable insight into the mechanisms that link all these risk factors to atheroma development and the clinical manifestations of this disease.(41)(42)

1.5. **Diagnosis**

**1-Blood tests.** Blood tests are usually done to check blood sugar and lipid profile levels. High levels of blood sugar and cholesterol raise the risk of atherosclerosis. A C-reactive protein (CRP) test also may be done to check for a protein linked to inflammation of the arteries.

**2-Electrocardiogram (ECG or EKG)**. This quick and painless test measures the electrical activity of the heart. During an ECG, sensors (electrodes) are attached to the chest and sometimes to the arms or legs. Wires connect the sensors to a machine, which displays or prints the results. An ECG can help determine if there's reduced blood flow to the heart.

**3-Exercise stress test** If your symptoms usually occur during exercise, your health care provider may recommend this test. You'll walk on a treadmill or ride a stationary bike while your heart is monitored. Because exercise makes the heart pump harder and faster than it does during most daily activities, an exercise stress test can show heart problems that might otherwise be missed. If you can't exercise, you may be given a medication that mimics the effect of exercise on your heart.

**4-Echocardiogram**. This test uses sound waves to show blood flow through the heart. Sometimes it is done with exercise stress testing.

**5-Doppler ultrasound**. Your provider may use a special ultrasound device (Doppler ultrasound) to measure your blood pressure at various points along your arm or leg. These measurements can show the speed of blood flow in the arteries.

**6-Ankle-brachial index (ABI).** This test compares the blood pressure in the ankle with that in the arm. It's done to check for atherosclerosis in the arteries in the legs and feet. A difference between the ankle and arm measurements may be due to peripheral vascular disease, which is usually caused by atherosclerosis.

**7-Cardiac catheterization and angiogram.** This test can show if the coronary arteries are narrowed or blocked. A long, thin flexible tube (catheter) is inserted in a blood vessel, usually in the groin or wrist, and guided to the heart. Dye flows through the catheter to arteries in the heart. The dye helps the arteries show up more clearly on images taken during the test. (43)(44)

**Aims of Study**

The aims of the study:

1- Investigating the role of the relationship between Lipid profile associated Atherosclerosis patients.
2- Values of TG/HDL and LDL/HDL ratios in atherosclerotic disease
3- Prove that LDL/HDL ratio which combines the two variables is better than either LDL-C or HDL-C alone in predicting atherosclerotic severity, as an independent risk factor for atherosclerosis

## 2-Material and Methods

### 2-1- Blood Collection

Blood serum samples were collected from Al-Furat Al-Awsat Oncology Hospital .

During the time period from 1/10/2022 to 1/2/2023 .

Samples were collected for male patients in the range less than **45** years .

## 2-2- MATERIAL

| No | Item | Company |
|---|---|---|
| 1- | Spectrophotometer | Lab tech. China |
| 2- | Pipettes | Hettich, China |
| 3- | Tubes | China |
| 4- | Alp kit | Human,China |
| 5- | TG kit | Human,China |
| 6- | Cholesterol kit | Human,China |
| 7- | HDL kit | Human,China |

**Table 2-1:Materal blood collection**

## 2-3- METHODS

### 2-3-1-Procedure of TG

1-wavelength 505 nm (490-550); Temperature 37°C/15-25°C; Cuvette 1cm path.

2- adjust the instrument to zero with distilled water.

3- pipette into a cuvette:

| | Blank | Standard | Test |
|---|---|---|---|
| Standard | ----- | 10micro L | ------ |
| Sample | ----- | ---------- | 10 micro L |
| Working reagent | 1ml | 1ml | 1ml |

Mix, incubate 5 min at 37°C or 10 min at room temperature. Read the absorbance of sample and standard against blank . The color is stable for at least 30 min .

TG = ( Absorbance of sample / Absorbance of standard ) × conc. Of standard

2-3-2-Procedure of cholesterol

| Tubes | Blank | Standard | Test |
|---|---|---|---|
| Working reagent | 1 ml | 1 ml | 1ml |
| Blank | 10 micro L | --------- | ------- |
| Specimen | ---------- | 10 micro L | ------- |
| Standard | ---------- | --------- | 10 micro L |

Mix and incubate the tubes 10 min at room temperature or 5 min at 37°C .

Read the absorbance of the sample and standard at 500 nm against the reagent blank.

The color is stable for at least 30 min protected from light .

Total cholesterol = ( Absorbance of sample / Absorbance of standard ) × conc. Of standard

2-3-3-Procedure of HDL , LDL , VLDL

1- (500 micro L of serum ) + 50 micro L of cholesterol reagent , wait for 15 min
Then centrifuge to remove lipid complex .

2- 1 ml of HDL reagent + 25 micro L of supernatant , wait for 5 min
Then read by spectrophotometer .

3- Absorbance is measured at 600 nm.

4- Normal value : > 35 mg / dL (0.9 mmol / L )

HDL = ( Absorbance of sample / Absorbance of standard ) × conc. Of standard

VLDL = TG / 5

LDL = Total cholesterol – ( HDL + VLDL )

## 3- DISCUSSION

We found a relationship between the extent of atherosclerosis disease and lipid variables using univariate analysis, the ratio of triglycerides to HDL-cholesterol was found to be a powerful independent indicator of extensive atherosclerosis disease. According to t-test the mean TG/HDL ratio in Atherosclerosis patient's blood compared to healthy people blood are shown in table (3-1).

**Table 3-1: Statistically concentration of Mean and Standard Division and Mean and Standard Error TG/HDL**

| | Healthy | patients |
|---|---|---|
| Mean | 2.004 | 12.56 |
| Std. Deviation | 0.9035 | 4.196 |
| Std. Error of Mean | 0.1807 | 0.8392 |
| Lower 95% CI | 1.631 | 10.83 |
| Upper 95% CI | 2.377 | 14.30 |

The results obtained prove that the TG/HDL is high in blood with atherosclerosis patients, compared to its concentration in healthy blood (significantly $p<0.001$ raised). figure(3-1) evident that

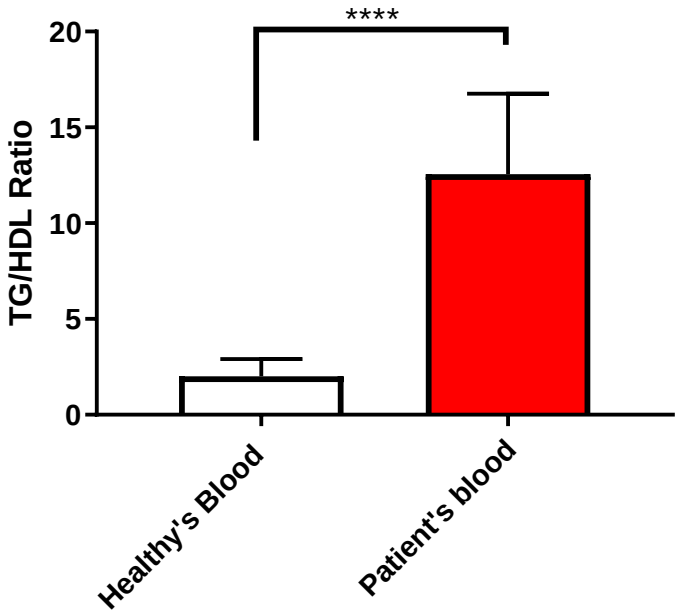


**Figure 3-1 TG/HDL Ratio in atherosclerosis patients**

The present study indicates that TG/HDL-c, which we previously showed to be an indicator of the development of atherosclerosis disease development (45) is also related to the severity of vessel compromise. Thus this ratio is an easy, non-invasive means of predicting the presence and extent of atherosclerosis

The occurrence and development of atherosclerosis result from multiple factors. Dyslipidemia, as a known risk factor, promotes and aggravates atherosclerosis. Increasing evidence shows that the decrease of HDL and the increase of LDL may be involved in the progression of atherosclerosis and promote the development of atherosclerosis [46–47]. Elevated LDL level is an independent predictor of atherosclerotic cardiovascular disease. LDL, increased HDL level can effectively slow down atherosclerosis and reduce the occurrence of atherosclerosis-related diseases [48]. Consistent with these results, our study shows the level of LDL is higher and the level of HDL is lower in atherosclerosis group than those in healthy group.

**According to t-test the mean LDL/HDL ratio in Atherosclerosis patient's blood compared to healthy people blood are shown in table (3-2).**

| | Healthy | Patients |
|---|---|---|
| Mean | 1.928 | 3.150 |
| Std. Deviation | 0.5863 | 0.7548 |
| Std. Error of Mean | 0.1173 | 0.1510 |
| Lower 95% CI | 1.686 | 2.838 |
| Upper 95% CI | 2.170 | 3.462 |

A number of clinical studies have shown that in addition to single blood lipids, elevated LDL/HDL is a risk factor for atherosclerosis [49, 50]. In accordance with the results of previous studies, observation on 100 participants, shows that the LDL/HDL ratio in atherosclerosis group was higher than that in healthy group. Our study shows that LDL/HDL ratio which combining the two variables is better than either LDL or HDL alone in predicting atherosclerotic severity, as an independent risk factor for atherosclerosis.[51-52]

**The results obtained prove that the LDL/HDL is high in blood with atherosclerosis patients, compared to its concentration in healthy blood (significantly $p<0.001$ raised). figure(3-1) evident that**

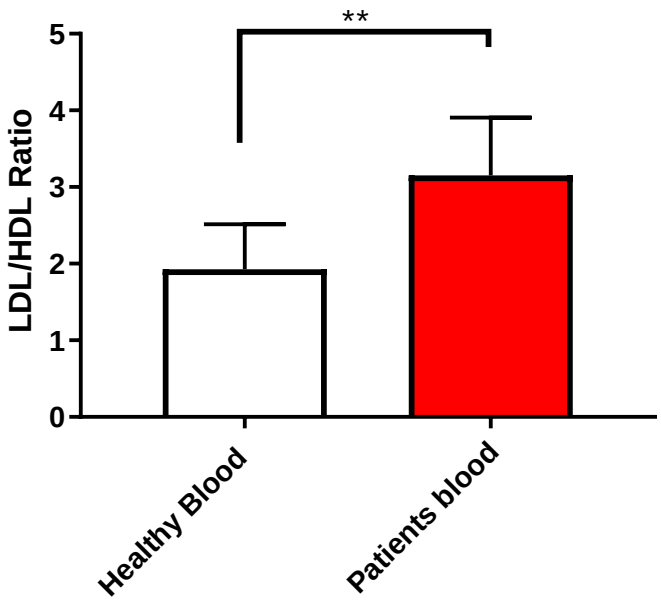


**Figure 3-2 LDL/HDL Ratio in atherosclerosis patients**

We studied a high-risk subset of patients, who showed a higher prevalence of atherosclerosis disease than the general population. We compared only lipid variables, and did not take into account the current use of medication or the inflammatory state of the patients.

## CONCLUSION

Nearly all routinely assessed lipid variables were associated with the extent of coronary disease, but only the ratio of triglycerides to HDL-cholesterol or to HDL-c were robustly associated with disease extent. Elevation in the ratio of TG to HDL-c was the single most powerful predictor of extensive coronary heart disease among all the lipid variables examined.

LDL/HDL ratio played an essential role in CAHD, acting as a representative of CAHD severity. LDL/HDL ratio has higher specificity and sensitivity than the single indicator LDL-C or HDL-C. Adding LDL/HDL to traditional risk factors can further improve the comprehensive judgment index for the occurrence of coronary atherosclerosis. LDL/HDL ratio may identify early patients with atherosclerosis or high-risk individuals for CAHD, guiding primary prevention strategies for CAHD

Recommendation

1- Study the project from a genetic point of view
2- Study the effect of smoking on these measured ratios and its effect on atherosclerosis
3- Statement of the effect of obesity on atherosclerosis

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