# Hyperlipidemia: pathophysiology, causes, complications, and treatment. A review

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### Abstract

Hyperlipidemia is a common disease around the word affected both developed and developing countries, in this disease blood level of lipids is elevated more than normal range. Elevated lipids levels (cholesterol, fats, and triglyceride) predispose the patient to a various serious and sometimes lethal complications such as cardiovascular disease, cerebral strokes, hepatic and renal dysfunction. This disease usually asymptomatic and the patient discover the disease by routine blood analysis. At the advanced stages of the disease, patients may suffer multiple complications such as hypertension and angina. There are two major types of hyperlipidemia. The first type is the primary hyperlipidemia which is usually familial type caused by genetic abnormalities. The other type is called secondary hyperlipidemia which is resulted from predisposing factors like obesity, thyroid dysfunction, alcoholism, drugs (B-blockers), hypothyroidism, and chronic renal failure.

Hyperlipidemia could be treated either by changing life style and follow a healthy behavior or by using medications (hypolipdimic agents) or both to reach the therapeutic goal which is controlled blood lipid levels. On other hand, huge number of medicinal plant extract where tested and show significant advantage in controlling blood levels of lipids. This review article will discuss this disease and different types of hypolipdimic agents.

Key words: Hyperlipidemia, Hypolipdimic agents, complications, cardiovascular disease.

Abbreviations: CVD: cardiovascular disease, LDL: low density lipoprotein, HDL: high density lipoprotein.

Conflict of interest

The authors declare that they have no conflicts of interest.

الكلمات المفتاحية: زيادة نسب دهون الدم، الادوية المهبطة لمستويات الدهون، امراض القلب والاوعية الدموية.

الخلاصة

ارتفاع دهون في الدم هو مرض شائع حول العالم في الدول المتطورة والنامية ، يحدث عندما تكون مستويات دهون الدم بانواعها (الكوليسترول، الدهون الثلاثية، الشحوم) اكثر من المستويات الطبيعية. ان هذا الارتفاع بمستويات الدهون يؤدي الى مضاعفات خطرة على المريض وفي بعض الاحيان مميته. و منها امراض القلب والاوعية الدموية.

هذا المرض عادة يكون بدون اعراض او علامات ويكون اكتشافه وتشخيصه عن طريق الفحوصات الروتينية للدم . خلال المراحل المتقدمة من المرض قد يعاني المريض من بعض المضاعفات مثل ارتفاع ضغط الدم والذبحات الصدرية. هناك نو عان من المرض، النوع الاول يسمى الاولي وسببه عادة ما يكون وراثي اما النوع الثاني فيسمى عادة بالثانوي وذلك لانه يكون نتيجة وجود سبب اخر مثل السمنة، اعتلال الغدة الدرقية، الادمان على الكحول، الادوية (مثال: قافلات مستقبلات بيتا)، خمول الغدة الدرقية، واعتلال الكلى المزمن.

ارتفاع نسب شحوم الدم يمكن معالجته اما بتغيير سلوكيات الفرد واتباع اسلوب حياتي صحي دائمي او باستخدام الادوية (خافضات الدهون) او كليهما للحصول على الهدف العلاجي و هو ارجاع مستويات الدهون الى الحدود الطبيعية. من جهة اخرى فقد تمت در اسة العديد من النباتات الطبية التي اظهرت نتائج ايجابية جيدة في السيطرة على مستويات دهون الدم واعادتها الى المستويات الطبيعية. سيتناول هذا المقال شرحا وافيا لهذه الحالة المرضية وطرق علاجها وانواع الادوية الخافضة للدهون.

### Introduction

The term hyperlipidemia means that the level of blood lipids (fats, cholesterol, and triglycerides) is elevated more than normal leading to a dangerous complications [1]. These complications are usually related to the formation of atherosclerosis and its related disorders such as cardiovascular disease, peripheral vascular disease, cerebrovascular disease, and brain strokes [2]. The deposition of these lipids (especially cholesterol) in the arteries walls resulting in narrowing of these vessels and insufficient blood flow through the affected vessels [3] and formation of atherosclerosis as seen in figure 1. Morbidity and mortality rates increased when there are other prevalent diseases like hypertension, diabetes mellitus, and renal disorders [4].



Figure 1: effect of high lipid levels on blood flow

https://www.dreamstime.com/stock-image-atherosclerosis-artery-image19987221

Globally, there were 14.4 million deaths by cardiovascular diseases in 1990 and increased to 17.5 million in 2005, and in 2015 the number expected to be 20 million [5]. Therefore, dyslipidemia was considered the main risk factor of cardiovascular diseases and deaths. Hyperlipidemia is classified by two main systems. The first system classify this pathological condition into primary and secondary, the primary class is familial caused by genetic abnormalities, while secondary class which resulted by

underlying causes often called acquired. The second system of classification is depending on the type of elevated lipid such as hypercholesterolemia, hypertriglyceridemia, and hypolipoproteinemia [6].

Hyperlipidemia causes includes: obesity, type II diabetes mellitus, thyroid dysfunction, alcoholism, renal diseases, jaundice, hormonal therapy, mutation in lipoprotein lipase, and medications such as diuretics, B-receptor blockers and cyclosporine[7] in addition to other causes as showed in (Table 1).

Conditions causes hypertriglyceridemia	Conditions causes hypercholesterolemia
acromegaly	Anorexia nervosa
alcoholism	Cholestasis
Burns	Cushing's syndrome
Chronic renal failure	Growth hormone deficiency
Diabetic mellitus	Hypothyroidism
Glycogen storage disease	Nephrotic syndrome
Lipodystrophy	Obstructive liver disease
Obesity	

### Table1: causes of secondary hyperlipidemia

The signs and symptoms of hyperlipidemia may be not noticeable and the patient discovers this disorder by routine blood tests. In general, patient may suffer chest pain, abdominal pain, hepatic enlargement, spleen hypertrophy, heart diseases, and athermanous plagues in blood vessels [8]. Other symptoms of dyslipidemia are illustrated in(figure 2).



Figure 2: signs and symptoms of hyperlipidemia

## Pathophysiology of hyperlipidemia

Because of its serious complications and the increased rates of mortality and morbidity of hyperlipidemia, huge number of studies and scientists tried to explain the exact pathophysiology of the disease with more specific details. This is in order to achieve diagnosis and active treatment at early disease stage to prevent complications and improve patient health. According to the present studies and reviews, hyperlipidemia is started from endothelial damage of the blood vessels, leading to the loss of nitric oxide in the damaged site, this will be resulting in increase in the inflammatory response around the affected area and accumulation of the lipids in the deepest layer of the endothelial wall, macrophage cell will engulf the lipids forming what is called (the foam cell) with cholesterol content as shown in (figure 3). The formation of foam cell will cause necrosis, apoptosis, and mitochondrial dysfunction. At the same time, the cells of the smooth muscle encapsulate the foam cell producing fibrotic plague and inhibit destroying of the foamy cells. On other hand, stimulation of the platelets activity with the tissue factors resulting in plague rupturing and thrombosis as in (figure 4). Development of plague occur either rapidly resulting in obstruction of the blood vessels or slowly that cause stenosis of the blood vessels. In both mechanisms, lipid plague remains the mainstay of the development of CVD and deterioration of patient health status.

In addition to the CVD, patients with hyperlipidemia can also suffer from tendon dysfunction especially patellar tendon. This is because with time hyperlipidemia will produce higher number of macrophages in the tendon tissues, collagen fiber damage and replaced by lipid instead of collagen resulting in less effective tendons that are exposed to harm easily[9].



Figure 3: formation of foamy cells [10]



Figure 4: activation of platelets and tissue factors resulting in formation of thrombosis [10].

## **Treatment of hyperlipidemia**

## 1. Life style changing

The first line in the treatment of hyperlipidemia before staring medications is changing life style of patient and trying to make it healthier. Starting these steps will have crucial role in some patient and may don't need to use hypolipdimic drugs and will save patients form their side effects. These changes include: regular exercise like walking or some light sports, weight control for patient with overweight or obese, minimizing the use of cholesterol and fats in their daily food, reduce alcohol consumption and quit smoking [11] [12]. On other hand, adding some healthy food like cold-water fishes (i.e. sardines and salmon) to the daily food help to reduce the level of triglycerides because of their Omega-3 contents. Similarly, soybeans and soy nut contain antioxidant agents that can lower the level of bad cholesterol[12].

## 2. Pharmacological treatment of hyperlipidemia

Lipid lowering agents are used when changing life style (first line) is failed to reduce blood lipid levels.

Hypolipdimic agents could be classified to five main groups:

## HMG-CoA reductase inhibitors (statins):

The first family of lipid lowering agents and have a good evidence in reducing the level of LDL-cholesterol and thereby reducing cardiovascular complications of hyperlipidemia in both animals and humans. It was used since 1970s for primary and secondary prevention of CVS complications[13].

Statins act by competitive inhibition of Hydroxyl- methyl glutaryl coenzyme-A (HMG-CoA) which is the limiting step in the cholesterol biosynthesis resulting in low level of LDL and blood lipids in general [14] as shown in (figure 5). Studies demonstrated that

statins have also role in reducing C-reactive protein (inflammatory marker). Therefore, it have anti-inflammatory effects especially after myocardial infarction caused by high lipid level and have greater clinical benefits in cardiac problems prognosis and managements [15]. In addition, it could be used in the treatment of rheumatoid arthritis, Parkinson disease, and sclerosis.

Despite the previous clinical uses of statins, it's used record some adverse effects such as myalgia and predispose to type II diabetes mellitus. But it still the mainstay in the treatment of high blood lipids levels[16].

The members of this family include atorvastatin (Lipitor), fluvastatin( lesxol XL), lovastatin(Altoprev), pitavastatin (livalo), pravastatin(Pravachol), rosuvastatin (Crestor, Ezallor) and simvastatin(Zocor) [13].



Figure 5: Statins and the cholesterol synthesis pathway – the mevalonate pathway .[17]

Bile acid sequestering agents (Resins)

Approved by Food and Drug Administration to be used in patient who are unable to use statins because of their side effect or used in combination with statin to achieved the required goal[18].

These agents are safe to be used in children (less than 17 years old) who have high blood level of cholesterols and also in pregnant women. In addition, bile acid sequestering could be used to treat diarrhea and itching resulting from high level of bile acids [19, 20].

This group includes three members (colesevelam, colestipol, and cholestyramine) they could be used as a single therapy or as adjuvants agent with other hypolipdimic medications.

Bile acid sequestering reduces the concentration of LDL-cholesterol by inhibiting the absorption of bile acids from the intestine and formed indigestible complexes that are excreted with feces. Reduction in bile acid concentration leading to reduce in cholesterol level through the liver because hepatic cholesterol will be converted to bile acids due to blocking of 7-alpha hydroxyl coenzyme (the rate limiting step in acid biosynthesis) [21]. The final results is lowering in cholesterol level and increase in the number of LDL-receptors within the liver and finally low LDL-concentration in the blood[18] as in (figure 6).

There are some studies demonstrated that these agents can increase the concentrations of hepatic cholesterol by increasing the activity of Glutaryl-Coenzyme A, but the newly formed cholesterol will not reach the blood circulation since it will directed for bile acid synthesis pathway.

Side effects of these agents are not serious since they are not absorbed form the intestine, but still have minor gastrointestinal adverse effect such as constipation (28% of cholestyramine taken patient), vomiting, gastric upset, and appetite losing [22].



Figure 6: mechanism of action of resins slideplayer.com/slide/13231846

### Active lipoprotein lipase (fibric acid derivatives)

Fibrates are the recent example of this family, they include three members (gemfibrozil, bezafibrate, and fenofibrat). Fibrates have the ability to reducing the blood levels of triglycerides by increasing lipoprotein lipase activity. The mechanism of action of fibrates was well studied and understood, the induction of lipoprotein lipase enzyme resulting in conversion of triglycerides to glycerol and fatty acids. The produced fatty acids then stored in the adipose tissue or used in the skeletal and cardiac muscle as a fuel. Activation of lipoprotein lipase enzyme by fibrate coming from their ability to cause mutation in the gene transcription which leads to activations of peroxisome proliferator-activated receptor alpha. Ultimately, induction of lipoprotein lipase enzyme [23]

These agents have a clinical significant in cardiac disease treatment and reducing higher levels of cholesterol in addition to its role in reducing atherosclerosis event and improving insulin sensitivity [24]. Similar to other medicines, fibrate can produce side effects like renal impairment [25] and myositis especially when given together with statins or in patient with renal failure [26]. In general fibrates are well tolerated agents with beneficial clinical effects. Considerable number of studies demonstrated that fibrates have anti-inflammatory, anti-oxidant, and anti-thrombotic actions, makes these agents used in other disorders in addition to its hypolipdimic action.

Lipolysis and triglyceride synthesis inhibitors (nicotinic acid)

Nicotinic acid is water-soluble vitamin B3. These agents were used as a first line therapy of dyslipidemia since 1966. It was used as a monotherapy to improve patient health status who suffer dyslipidemia in order to reduce cardiac complications [27]. Nicotinic acid (niacin) produce its hypolipdimic effect by its ability to reduce LDL, VLDL, Triglyceride, and total cholesterol and increase HDL- cholesterol. The followup studies after administration of niacin showed that the mortality rate was reduced to a large extent. Similarly, niacin therapy provide an important secondary prevention of coronary heart disease to a significant rate [28]. With time, niacin side effects became unpleasant and not tolerated by the patient although they are harmless. These side effects include cutaneous flushing, gastrointestinal upset, diarrhea, and hepatotoxicity especially with sustained- release formula [29]. Elevated blood levels of uric acid also were reported in patients taken niacin. Therefore, new strategies were developed to minimize these drawbacks of this beneficial agent. These strategies include studying nicotinic receptor deeply and produce selective agent and develop a new formula composed of extended- release of niacin with laropiptran (prostaglandin D2 antagonist) with a clinical significant to reduce hyperlipidemia and flushing side effect by the action of laropiptran [30]. Niacin can prevent lipolysis process and reduce the concentration of fat and triglyceride in the blood stream [31] (figure 7).



Figure 7: Effect of niacin on blood lipids.

selfhacked.com/blog/top-science-based-health-benefits-vitamin-b3-niacin

### Ezetimibe

Ezetimibe is a recently approved drug to treat hypercholesterolemia, it produce its action through preventing the intestinal absorption of cholesterol by targeting the Nimann pick C1-like1 protein (a critical protein for intestinal cholesterol absorption). It could be used alone or in combination with statins (such as simvastatin) to produce a

better clinical outcomes [32]. Concomitant used of statins with ezitimibe reduce the level of cholesterol by about 23-24 % leading to decline in the risk factor of coronary heart diseases and improve patient health status[33].

### Guggal lipids:

Cholesterol and triglyceride levels in the blood were noted to decline after [12]continuous used of sterones mixture prepared from guggal gums

Hyperlipidemia in pharmacognosy

Increasing mortality and morbidity rates resulting from hyperlipidemias and their cardiovascular complications encourage the scientists to increase their attention in order to produce a number of drugs and alternative methods for treatment and prevention of these serious conditions. Medicinal plants with hypolipdimic characteristics are considered the most appropriate choice for patients who cannot take drugs or not respond to medications. Large number of plants were studied and approved to be used in hypolipdimic treatment and prevention.

Trachyspermum ammi was studied on albino rats and showed good antioxidant properties and decreased the levels of cholesterol, triglycerides, and low-density lipoprotei [34]. Aloe Vera also was studied and provided significant antihyperlipidemic action[35]. On other hand, aqueous extract of Camellia sinensis also was studied and its hypolipdimic activity was tested on rats and showed significant reductions in levels of blood lipids due to the presence of flavonoids and polyphenolic compounds which have antioxidant activity [36]. Other examples of plants with hypolipdimic activity includes ginger ethanolic extract[37] and Garcinia daedalanthera[38].

### Conclusion

Improvement of clinical tests and diagnosis methods make the discovery of any diseases easier and faster than previous decades. So that it is very important to advise patient with other disease or people who have familial history of hyperlipidemia to do routine lipid profile test regularly even they don't suffer any signs or symptoms of high blood lipids. This is very important to prevent and treat this serious disorder in a goal to prevent the development of complications such as cardiovascular disease which consider the primary cause of death globally. Considerable number of medications with significant safety could be prescribed by the physician depending on the degree of the disease and the health state of the patient. In addition, medicinal plants also have a role in the treatment of the disorder but this require a sufficient acknowledgment about the disease and the plant.

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