

## HYPERLIPIDEMIA- A DEADLY PATHOLOGICAL CONDITION

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## ABSTRACT

Cardiovascular diseases (CVDs) have been reckoned amongst the top reasons for early deaths in the country. One of the major risk factors for developing CVDs is hyperlipidemia, an elevated condition of lipid levels in the body. Hyperlipidemia has been known to speed up a process of hardening of the arteries called atherosclerosis that may prove fatal in the development of various CVDs. Lipids are the "fats" in the bloodstream that is commonly divided into cholesterol and triglycerides. There are many types of cholesterol that include total cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol. The anomalous increase in cholesterol levels may be attributed to unhealthy lifestyle, heavy alcohol use, pathological conditions like diabetes, renal disease and certain medications. Various treatments have been found suitable for treating hyperlipidemia that includes statins, niacin, fibric acid derivatives and cholesterol absorption inhibitors. This review explains about the classification and treatments for the hyperlipidemia.

**Keywords:** Cardiovascular, Hyperlipidemia, Cholesterol.

## INTRODUCTION

In 2002, CVDs contributed to approximately a third of entire global deaths, whereas, by the year 2020, it is expected that CVDs will become the leading cause of death and disability worldwide.<sup>1, 2</sup> At proper levels, lipids have been noted to perform important functions in the body, but may cause various health problems if present in excess amounts. The term hyperlipidemia refers to the elevated lipid levels in the body including high cholesterol and high triglyceride levels.<sup>3, 4</sup> Lipids have been considered as "fats" in the bloodstream, which is commonly divided into cholesterol and triglycerides. However, the cholesterol circulates in the bloodstream and is involved in the structure and function of cells, whereas, the triglycerides are either used immediately or stored in the fat cells.<sup>5, 6</sup> Further, High cholesterol levels in the body have been considered as a modifiable risk factor which is evident by the fact that plasma cholesterol at levels >200 mg/dL cause 4.4 million deaths in a year.<sup>7</sup> <sup>8</sup> Various types of cholesterol have been reported that include total cholesterol (TC), consisting of all the cholesterol combined; HDL cholesterol, often referred to as good cholesterol; and LDL cholesterol, often called bad cholesterol.<sup>9, 10</sup> The abnormal cholesterol levels are the result of an unhealthy lifestyle including taking high-fat diet and other lifestyle factors like being overweight, heavy alcohol use and lack of exercise.<sup>11</sup> Moreover, diabetes and underactive thyroid gland have also been reported to cause high cholesterol levels.<sup>12, 13</sup> Other illnesses that may elevate cholesterol levels include polycystic ovary syndrome and kidney disease. The higher levels of female hormones like estrogen, have been noted to increase or change cholesterol levels. In addition, drugs like diuretics, beta-blockers and medicines used to treat depression have also been reported to raise cholesterol levels.<sup>14</sup> Numbers of studies have shown statins, niacin analogues, fibrates, bile acid binding resins and cholesterol absorption inhibitors to possess certain modulatory roles in the treatment of hyperlipidemia.<sup>15-18</sup> The present review highlights about the classification of cholesterol. Moreover, various strategies for the treatment and prevention of hyperlipidemia have been critically discussed in the review.

## CLASSIFICATION OF LIPID CONCENTRATIONS

It has been noted that cholesterol along with some other types of fats cannot be dissolved in the blood. Moreover, in order to be transported to and from cells, they have to be specially carried by certain molecules called lipoproteins, which consist of an outer layer of protein with an inner core of cholesterol and triglycerides.<sup>19, 20</sup> In addition, the lipoproteins have been found essential for cholesterol to move around the body. The lipids can be classified as TC, triglycerides, LDL, HDL and very low density lipoprotein (VLDL) cholesterol.

**Total cholesterol:** According to guidelines of National Cholesterol Education Program (NCEP), TC concentrations below 200 mg/dL have been regarded as desirable, whereas, concentrations greater than 240 mg/dL are referred to as hyperlipidemic. However, epidemiological evidence suggests that the risk of cardiac events decreases as TC levels fall approximately to 150 mg/dL. Moreover, TC should be less than 180 mg/dL for children.<sup>21-23</sup>

**Triglyceride:** Triglycerides are another type of fat that is carried in the blood by VLDL. Moreover, it has been shown that excess calories, alcohol or sugar in the body get converted into triglycerides and stored in fat cells throughout the body.<sup>24</sup> The triglyceride concentration less than 150 mg/dL is regarded as normal, whereas, concentrations of 200-499 mg/dL are considered as high. Moreover, concentrations of 500 mg/dL or higher are considered dangerous for the development and progression of various CVDs.<sup>22</sup>

**LDL cholesterol:** LDL is commonly known as the bad cholesterol, which is produced by the liver and carry cholesterol and other lipids from the liver to different areas of the body like muscles, tissues, organs and heart. The high levels of LDL indicate much more cholesterol in the blood stream than necessary and hence, increase the risk of heart disease.<sup>21, 25</sup> According to NCEP guidelines, LDL cholesterol concentrations below 100mg/dL are considered optimal, whereas concentrations in the range of 160-189 mg/dL are considered to the higher side.<sup>25</sup> However, increasing evidence supports that normal human LDL cholesterol concentration can be as low as 50 to 70 mg/dL.<sup>22</sup> Moreover, it has been comprehensively seen that the risk of CVDs decreases as LDL cholesterol concentration decreases.

**HDL cholesterol:** HDL is commonly referred to as the good cholesterol, which is produced by the liver to carry cholesterol and other lipids from tissues back to the liver for degradation.<sup>26</sup> High levels of HDL cholesterol have been considered as a good indicator of a healthy heart. The concentrations of 60 mg/dL or higher have been considered as optimal, whereas, HDL concentrations below 40 mg/dL are considered as major risk factor for CVDs. However, HDL is often interpreted in the context of TC and LDL concentrations, and hence may be regarded as less significant when LDL is low.<sup>22, 26</sup>

**VLDL Cholesterol:** VLDL is similar to LDL cholesterol in the sense that it contains mostly fat and not much protein. VLDL cholesterol is the lipoproteins that carry cholesterol from the liver to organs and tissues in the body.<sup>27</sup> They are formed by a combination of cholesterol and triglycerides. Moreover, VLDLs are heavier than LDL, and are also associated with atherosclerosis and heart disease.<sup>27</sup>

## RISK FACTORS ASSOCIATED WITH HYPERLIPIDEMIA

A variety of risk factors have been found to be associated with hyperlipidemia like cholesterol rich food, overweight, alcohol abuse, diabetes and stress.<sup>28</sup> Saturated fat and cholesterol in the food has been noted to increase cholesterol levels in the body. Further, in addition to being a risk factor for heart disease, being overweight also increases the cholesterol levels in the body. Moreover, it has been shown that losing weight can help lower LDL and total cholesterol levels and consequent increase the HDL cholesterol levels in the body.<sup>29</sup> In addition, regular exercise has also been noted to lower LDL cholesterol and raise HDL cholesterol levels. Another modifying factors in the development and progression of hyperlipidemia are age and gender. It has been shown that cholesterol levels rise as the person gets older.<sup>28-30</sup> However, before menopause, women tend to have lower TC levels than men of the same age, whereas, after menopause, LDL levels of women tend to rise.<sup>31</sup> Furthermore, it has been comprehensively suggested that poorly controlled diabetes leads to increased cholesterol levels. The improvements in diabetes control have been demonstrated to decrease the cholesterol levels in the body.<sup>32</sup> Heredity has also been a modifying factor for the progression of hyperlipidemia as it has been noted that the genes partly determine the amount of cholesterol body makes. Surprisingly, it has been reported that moderate alcohol intake increases HDL-cholesterol. However, it is not known whether it also lead to reduction in the risk of heart disease, but drinking too much alcohol has been noted to damage the liver and cardiac muscle ultimately leading to other health problems.<sup>33</sup> The modifying role of stress in the development and progression of hyperlipidemia has been confirmed by the fact that people under stress have been shown to console themselves by eating fatty foods ultimately leading to hyperlipidemic condition.

## PATHOPHYSIOLOGY OF HYPERLIPIDEMIA

The pathophysiology of hyperlipidemia can be studied under two headings, i.e., primary hyperlipidemia and secondary hyperlipidemia. The pathophysiology of primary hyperlipidemia involve that the idiopathic hyperchylomicronemia defect in lipid metabolism leads to hypertriglyceridemia and hyperchylomicronemia which is caused by a defect in lipoprotein lipase activity or the absence of the surface apoprotein CII.<sup>34</sup> Further, in primary hyperlipidemia, the LDL cholesterol is high which is supported by the results obtained in various studies showed that idiopathic hypercholesterolemia occur in many families of doberman pinschers and rottweilers.<sup>34, 35</sup> Moreover, hyperchylomicronemia in cats with autosomal recessive defect in lipoprotein lipase (LPL) activity showed the occurrence of primary hyperlipidemia.<sup>36</sup>

In secondary hyperlipidemia, the postprandial absorption of chylomicrons from the gastrointestinal tract occurs 30-60 min after ingestion of a meal containing fat that may increase serum triglycerides for 3-10 hours.<sup>37</sup> The diabetes mellitus patients have been noted to possess low LPL activity which further caused high synthesis of VLDL cholesterol by the liver ultimately leading to hyperlipidemia. Moreover, hypothyroidism-induced low LPL activity and lipolytic activity has been noted to reduce hepatic degradation of cholesterol to bile acids. Furthermore, hyperadrenocorticism increased the synthesis of VLDL by the liver causing both hypercholesterolemia and hypertriglyceridemia.<sup>37, 38</sup> Liver disease hypercholesterolemia has been noted to be caused by reduced excretion of cholesterol in the bile. Furthermore, in nephrotic syndrome, the common synthetic pathway for albumin and cholesterol causes low oncotic pressure ultimately leading to enhanced cholesterol synthesis.<sup>39, 40</sup>

## TREATMENT OF HYPERLIPIDEMIA

Presently, medications from five major classes of drugs have been reported to treat people with detrimental lipid levels that include statins, nicotinic acid derivatives, fibric acid derivatives, bile acid binding resins and cholesterol absorption inhibitors (Fig.1).<sup>16-18</sup> Statins, the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, are the medications that have been noted to inhibit the rate at which cholesterol is formed in the body. Moreover, statins have also been reported to help draw cholesterol to the liver for

excretion.<sup>41</sup> However, statins have been associated with most common side effects like stomach upset, nausea, vomiting, headache and dizziness. The potent members of statins class of drugs include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin.<sup>42, 43</sup> The second class of agents that have been well reported for the treatment of hyperlipidemia is niacin that has diverse actions affecting cholesterol formation. The chief effect of niacin and its derivatives involves the decreased production of triglycerides in the body. Further, nicotinic acid has also been noted to raise HDL cholesterol levels via unknown mechanisms.<sup>44</sup> The common side effects of niacin drugs include flushing, hot flashes, itching and headache. The third potent class of agents for the treatment of hyperlipidemia is fibric acid derivatives which have been thought to reduce the formation and increase the breakdown of cholesterol and triglycerides in the body, accounting for their hypolipidemic potential.<sup>45</sup> Common side effects of this class of drugs are heartburn and stomach pain which have been noted to decrease over time. The potent members of fibrates are clofibrate, fenofibrate and gemfibrozil.<sup>45, 46</sup> Another class of agents for the treatment of hyperlipidemia involves bile acid binding resins, which are regarded as the medications that bind with bile acids, preventing the intestine from recycling them.<sup>47</sup> The liver responds by producing more and pulls cholesterol from the blood after sensing the decrease in bile acids. The common side effect of this drug is constipation. The potent members of the class include cholestyramine, colestipol and colesevelam.<sup>48</sup> Furthermore, cholesterol absorption inhibitors have also been reported for the treatment of hyperlipidemia which help reduce LDL levels by blocking absorption of cholesterol in the small intestine. Moreover, these drugs have been used in concurrence with a program including eating a low-fat/low-cholesterol diet, exercising and managing weight.<sup>49</sup> However, the class of drugs have been associated with certain side effects like headache, dizziness, stomach upset, joint pain and upper respiratory infections. The potent member of cholesterol absorption inhibitors is ezetimibe. Moreover, Vytorin, a combination medication containing simvastatin and ezetimibe, has been shown to reduce LDL cholesterol to a greater extent than statin therapy alone.<sup>50</sup> Additional studies are needed to provide more information about the safety and efficacy of Vytorin.

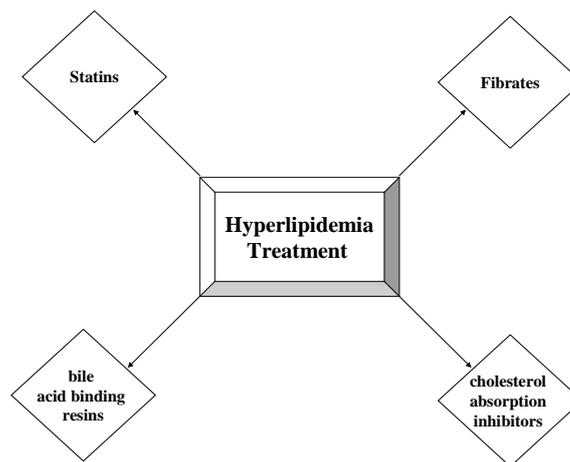


Fig. 1: Diagram Showing Treatment Strategies for Hyperlipidemia

## CONCLUSION

Hyperlipidemia is a critical condition of elevated lipid levels in the body that ultimately lead to the development and progression of various CVDs. The link between hyperlipidemia and occurrence of CVDs has already been established. Various studies have reported the treatment of hyperlipidemic patients with statins, fibrates and nicotinic acid derivatives. Moreover, the focus on dietary management should be done in order to prevent and treat the patients presented with hyperlipidemia. However, ample studies have provided the evidence for the efficacy of already reported treatments, but further studies are mandatory in order to provide more information about the safety and efficacy of novel antihyperlipidemic agents.

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