Mechanisms of Myocardial Damage Due to Hyperlipidemia: A Review of Recent Studies

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Myocardial injury and necrosis caused by hyperlipidemia have been investigated by several researchers. Their pathogenesis and molecular basis are different from those of the more common clinical ischemic myocardial injury. Hyperlipidemia leads to peroxide accumulation in the cardiomyocytes, causes lipid overload, decreases the antioxidant capacity of the body, and promotes the inflammatory response. Furthermore, hyperlipidemia causes changes in the structure and function of mitochondria in the cardiomyocytes, which results in their injury and necrosis. Many previous studies have shown that metabolic diseases (e.g., obesity and diabetes) and chemical poisoning can lead to hyperlipidemic myocardial injury and necrosis. Moreover, it has been observed that this pathological process can be inhibited by many small molecular substances. In the clinic, myocardial damage can be prevented or reduced by lowering the levels of triglyceride and cholesterol. Myocardial damage can also be regulated via the molecular pathway of myocardial injury caused by hyperlipidemia so that the disease can be treated. The present article reviewed the recent findings reported on the mechanisms of myocardial damage due to hyperlipidemia.

Keywords: Review • Hyperlipidemias • Heart Failure • Oxidative Stress

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Background

Hyperlipidemia refers to increased fasting triglyceride (TG) and/or total cholesterol (TC) in the blood. The condition can be subdivided into hypertriglyceridemia, hypercholesterolemia, mixed hyperlipidemia, and high levels of low-density lipoprotein (LDL). In terms of etiology, it can be divided into hyperlipidemia caused by genetic factors and non-genetic factors, also known as changeable factors and non-variable factors [1]. In recent years, researchers have also found that free fatty acids (FFAs), especially palmitic acid, play a key role in the mechanism of oxidative stress, iron death, and other areas of research [2,3].

Cardiomyocytes are damaged or even die to varying degrees depending on the disease state. Previous studies have shown that ischemic cardiomyopathy, hypertensive cardiomyopathy, and diabetic cardiomyopathy are the common causes of myocardial injury and necrosis [4,5]. Myocardial cell damage is also seen in hyperthyroidism, renal insufficiency, and viral myocarditis. The occurrence and development of the above-mentioned diseases are often accompanied by abnormal lipid metabolisms, such as dyslipidemia in patients with coronary heart disease and diabetes [6]. In recent years, some researchers have stated that myocardial cell damage can occur even when hyperlipidemia has not progressed to ischemic cardiomyopathy and is not accompanied by other metabolic diseases [7-9]. Hyperlipidemia is known to be associated with coronary artery disease due to atherosclerosis and ischemic heart disease. Recently, it was revealed that hyperlipidemia is also associated with an increased risk of non-ischemic heart failure, which can, however, be reversed by controlling the lipid levels [10].

Histopathological studies have demonstrated that disordered myocardial structure, cardiomyocyte fibrosis [11], and interstitial hemorrhage [12] can occur because of the influence of hyperlipidemia. A high-fat diet can induce cell apoptosis [13], ferroptosis, and autophagy [3,14], thus participating in various disease processes. From a biochemical perspective, a high-fat diet can induce the body’s inflammatory response [8], increase the production of reactive oxygen species (ROS) [15], down-regulate the expression of nuclear factor E2-related factor 2 (Nrf2) in the antioxidant system [7], and alter mitochondrial structure and function [7,16]. However, at present, the mechanism of the hyperlipidemia-induced inflammatory response is not completely understood. Comprehensive data are not available on cardiomyocyte apoptosis induced by pure hyperlipidemia [8], autophagy, and ferroptosis; hence, further research is needed. Since many diseases and lesions involve hyperlipidemia, a systematic and in-depth understanding of the pathogenesis of this condition and the mechanism of damage to the body can aid in the diagnosis and treatment of clinical diseases.

Table 1. Major mechanism of myocardial injury induced by hyperlipidemia.

| Major Injuries                  | Lipid         | Main reference |
|---------------------------------|---------------|----------------|
| Proinflammatory                 | LDL, oxLDL   | [21,26,30]     |
|                                 | FFA           | [40,41]        |
| Oxidative stress                | oxLDL         | [48-50]        |
|                                 | FFA           | [65]           |
| Metabolism decreased            | oxLDL         | [74,76]        |
|                                 | FFA           | [61-64]        |

LDL – low-density lipoprotein; FFA – free fatty acids; oxLDL – oxidized low-density lipoprotein.

Cardiac Lipid Accumulation

Glucose, fat, and ketone bodies are the main energy sources utilized for myocardial activity in the physiological state. The metabolic utilization of these energy substrates by myocardial tissues is significantly affected by the concentration of these substrates [17]. Under normal physiological conditions, the heart selects the corresponding substrates for energy metabolism in accordance with the amount of these energy substances, which more efficiently used the nutrients in the body and avoid the accumulation of a specific substance in the myocardium. Under certain pathological situations, such as obesity, metabolic syndrome, or ischemic cardiomyopathy, the utilization of fatty acids by the myocardial tissue decreases, leading to fat accumulation [18].

Lipid accumulation can induce pathological changes, such as inflammatory response, lipotoxicity, and cellular fibrosis, in the myocardial tissues [19]. These injuries caused by lipid accumulation in the myocardial tissues ultimately result in a decline in cardiac functions [20].

In the present review we discuss the myocardial damage induced by excessive lipid accumulation in terms of the proinflammatory response and decreased endoplasmic reticulum function and investigate the effect of high lipid concentration on the myocardial antioxidant capacity (Table 1).

Inflammatory Response Associated with Hyperlipidemia

Hyperlipidemia can alter the levels of inflammatory factors in the body. Some studies have shown that in the animal model of hypercholesterolemia, the level of plasma Cytokine-induced neutrophil chemokine-1 (CINC-1) increases, and the level of anti-inflammatory chemokine adiponectin decreases. On the contrary, the levels of inflammatory factors, such as CINC-1,
interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), in the myocardium decrease significantly, and the level of the anti-inflammatory factor adiponectin increases significantly [8]. The decrease of inflammatory factors and the increase of anti-inflammatory factors in the myocardium may be a self-protective mechanism of the cardiomyocytes in the early stages of hypercholesterolemia. To verify this conjecture, long-term animal experiments should be conducted on hypercholesterolemia to explore the changes in inflammatory and anti-inflammatory factors in cardiomyocytes after prolonged hypercholesterolemia. In vitro studies have shown that LDL and oxidized LDL (oxLDL) can promote expression of the IL-6 gene [21]. Some clinical prospective studies on chronic heart failure have shown that the levels of LDL and IL-6 in the disease group are higher than those in the control group. However, it is surprising that there was a negative correlation between IL-6 and LDL in the disease group [22]. The limitation of that study is that the nutritional status of patients with chronic heart failure was not considered. Except for the fact that patients with severe heart failure often experience disturbance in nutritional absorption [23], this negative correlation may be related to the fact that IL-6 promotes the expression of the LDL receptor (LDLR) gene. There is evidence that the activation of LDLR can promote the transfer of LDL from the blood to the vascular endothelium [24,25]. These studies have also observed that high cholesterol can cause an increase in IL-1, TNF-α, and C-reactive protein, which in turn leads to vascular endothelial inflammation [26]. Generally, high LDL can upregulate the expression of IL-6 in the body and the increased IL-6 can act on the IL-6 receptor (IL-6R) and activate its gene expression, thus promoting the internalization and degradation of LDL in the tissue cells [24]. Therefore, from the viewpoint of the target axis, by blocking the process of IL-6→IL-6R→LDLR, the transfer of LDL to the myocardium and endothelium can be reduced by inhibiting inflammation, but it will also reduce the degradation process of LDL. Related studies have also indicated that blocking IL-6R not only inhibits the inflammatory response but also leads to an increase in blood LDL levels [27,28]. Therefore, blocking this hyperlipidemic-inflammatory response without reducing the degradation of LDL is a promising research direction.

Peroxisome proliferator-activated receptor (PPAR) is mainly distributed in the adipocytes. Research advancements have provided more information on the functions and distribution of PPARs. Researchers have identified that PPAR and nuclear factor κB (NF-κB) mutually inhibit each other, thus playing an important role in anti-inflammation [29]. The level of LDL in the serum increases and the level of oxLDL increases accordingly, which can activate NF-κB [30]. After the activation of NF-κB, on the one hand, it promotes the de novo synthesis of cholesterol in the hepatocytes by inhibiting the AMPK pathway [31], and on the other hand, it inhibits the expression of PPARs. PPARs can reduce the level of TC7-hydroxylose (CYP7a1) in vivo [32]. Hence, the activation of NF-κB can promote CYP7a1 in this way. As a rate-limiting enzyme in bile acid synthesis, CYP7a1 plays a role in balancing the level of TC in the body [33]. Increased CYP7a1 can help the body convert excess TC into bile acid. To sum up, when the oxLDL level increases, on the one hand, it promotes the ab initio synthesis of TC via the NF-κB/AMPK pathway, and on the other hand, it promotes the metabolism of TC via the NF-κB/PPARs/CYP7a1 pathway. In this manner, a balance seems to be achieved, but this is not the case. Which of these 2 pathways is dominant in the body needs to be further researched. Moreover, it has been proven that activation of PPARs eventually leads to a decrease in the level of TC [34,35]. As mentioned earlier, PPARs and NF-κB inhibit each other, exert an anti-inflammatory effect, and inhibit the inflammatory response promoted by TNF-α and IL-6 [36]. CD36 can promote the uptake and degradation of oxLDL by the macrophages, but it leads to the formation of foam cells, which is considered to be one of the reasons why some PPAR activators increase the risk of coronary heart disease [37]. Other studies have reported that PPAR β/δ can inhibit foam cell production and inflammation [38]. There are 3 known subtypes of PPARs, and many ligands and functional contradictions exist. Hence, in-depth studies are needed on the specific mechanism and the drugs acting on this pathway [39].

Increased levels of TG in the blood also stimulate the body’s inflammatory response. After phagocytosis of lipids, foam cells formed by the macrophages participate in the inflammatory process of many diseases [40]. While TG promotes the activation of macrophages, excessive FFAs can induce inflammation and cause damage to multiple organs [41]. On the contrary, when the synthesis of TG is inhibited and the level of FFAs in the blood decreases, the phagocytosis of macrophages and the function of secreting inflammatory factors (IL-1 β, IL-6, and PGE2) is also inhibited [42] (see Figure 1 for the specific proinflammatory mechanisms of TC and TG).

**Hyperlipidemia Leads to Oxidative Stress**

It has been documented that the level of serum malondialdehyde increases in the animal model of hyperlipidemia, which suggests that hyperlipidemia could cause lipid peroxidation in vivo [8]. ROS are products of normal growth and metabolism in the body [43]; however, their excessive production causes oxidative damage to the tissues and participates in the aging of the body and the onset of many diseases [44]. ROS are also key factors that lead to oxidative stress injury in patients with hyperlipidemia. Various studies have shown that hyperlipidemia can increase the level of ROS and other oxides in organisms [13,45,46], thus causing damage to tissues and organs, including the myocardium.
ROS are usually produced during the oxidative phosphorylation of lipids by the mitochondria. The massive accumulation of ROS is often inseparable from the excessive activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) [47]. With the increase in the OxLDL level, ROS accumulation is induced by the oxLDL/receptor for advanced glycation end-product (RAGE)/NADPH oxidase NOX pathway [48]. It has been observed that oxLDL can also promote ROS production via lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) [49] and CD36 [50] pathways, all of which are a part of the NOX family. The accumulation of ROS triggered by high fat levels causes damage to the cells. In this process, the body’s response is often to produce antioxidants and antioxidative damage, but in cells with excessive damage, apoptosis or necrosis is induced [37]. NF-κB not only regulates inflammation but also exerts an antioxidant effect, and antioxidant enzymes, such as manganese superoxide dismutase, can be used as targets of NF-κB [43]. In the course of the disease, ROS inhibits the antioxidant pathway of NF-κB and also enhances the proinflammatory pathway of NF-κB [51].

Figure 1. Pathway diagram of hyperlipidemia leading to inflammatory response and oxidative stress. LDL – low density lipoprotein; FFA – free fatty acid; ROS – reactive oxygen species; Src – tyrosine-protein kinase Src; RAS – GTPase HRas; ERK – mitogen-activated protein kinase; P38 – P38 mitogen-activated protein kinase; VAV – guanine nucleotide exchange factor VAV; Rac – Ras-related C3 botulinum toxin substrate; Lyn – tyrosine-protein kinase Lyn; TXN – thioredoxin; GSH – glutathione; oxLDL – oxidized low density lipoprotein; LOX-1 – lectin-like oxidized low-density lipoprotein receptor-1; RAGE – advanced glycation end product receptor; CD36 – CD36 antigen; LDLR – LDL receptor; PPARs – peroxisome proliferators-activated receptors; HO-1 – heme oxygenase-1; NQO-1 – quinine oxidoreductase 1; NF-κB – nuclear factor-κB; Nrf2 – nuclear factor erythroid 2-related factor 2; TNF-α – tumour necrosis factor alpha; IL – interleukin.
has been observed that in the hyperlipidemic disease model established by a high-fat diet combined with Poloxamer 407 (P407) injection, the levels of antioxidants, such as Nrf2 and HO-1, were significantly lower than those in the control group, and the peroxidation reaction was increased. On the contrary, in the experimental group in which Nrf2 was activated, the oxidative damage of the target organs decreased significantly [58-60]. Unfortunately, the mechanism of hyperlipidemia inhibiting Nrf2 expression has not been further explored. We suspect that this may be due to oxidative damage causing excessive damage to the cells, which cannot effectively protect themselves against oxidation. However, this conjecture needs to be verified with more experiments, and its specific molecular mechanism and pathway need to be clarified. Hence, it is evident that a variety of cell injury and necrosis pathways are involved in oxidative stress. The study of antioxidation is an important link in the treatment of hyperlipidemic myocardial injury (see Figure 1 for the pathway of oxidative stress damage caused by high fat).

Changes in the Endoplasmic Reticulum and Mitochondria Caused by Hyperlipidemia

Researchers have stated that hyperlipidemia can damage mitochondrial function [61]. High fatty acid levels in the blood can promote the acetylation of mitochondrial fission protein power-related protein 1 (Drp1). In the intracellular environment of Drp1 acetylation, mitochondria exhibit structural ectopia and decreased function, which leads to myocardial dysfunction [62]. High fat can also affect the endoplasmic reticulum (ER). The accumulation of FFAs in the blood causes stress damage to the ER, which results in a decline in the metabolic capacity of the body and then affects the function of various organs and tissues [63]. Moreover, the accumulation of FFAs leads to the misfolding of ER molecular chaperones, which damages the structure and function of the ER [64]. High FFA levels increase ROS in vivo and participate in the process of ER injury [65]. It can be seen that the damage of ER and oxidative stress caused by hyperlipidemia are cross-linked.

FFAs are oxidized in the mitochondria to produce adenosine triphosphate, which provides energy for the body. Mitochondrial dysfunction can reduce the function of cardiomyocytes and eventually lead to a decline in cardiac function [66]. The metabolism of FFAs in the mitochondria is regulated by PPARs that promote this metabolic process [67,68]. The expression of PPARs is inhibited by NF-κB. When the expression of NF-κB increases, the expression of PPARs is inhibited, thus affecting the metabolism of FFAs and lowering the myocardial energy supply and cardiac function [69]. When the level of FFAs in the blood increases, their metabolism does not correspondingly increase, but activates NF-κB in the tissues [70,71], resulting in a decrease in the metabolic function of mitochondria toward FFAs. To change this pathological process, in addition to the various hypolipidemic schemes mentioned above, we can also promote mitochondrial metabolism and increase the myocardial energy supply by inhibiting NF-κB and activating PPARs, which improves cardiac functions [72].

As mentioned above, oxLDL also inhibits the function of PPARs by activating NF-κB, which undoubtedly affects the metabolic function of mitochondria toward FFAs. These findings suggest that NF-κB may be a key target to improve the mitochondrial dysfunction caused by hyperlipidemia. It is known that cholesterol in the body is transported to the liver for a series of metabolic processes. Cholesterol entering the liver is converted not only to bile acids but also to steroids in the mitochondria [73]. oxLDL clearly promotes the production of ROS, and excessive ROS leads to ER and mitochondrial stress, which in turn trigger the production of more ROS, thus affecting the metabolic function of the mitochondria [74]. Stress injury in the ER undoubtedly leads to further pathological damage to tissues and organs [75]. In severe cases, it causes a decline in the function of various organs, including the heart. In addition to the ROS pathway, oxLDL itself can induce ER stress and trigger a series of subsequent reactions, causing protein folding disorder and apoptosis. The specific pathway of ER stress leading to apoptosis is relatively complex and is not described in detail here. Hence, please refer to the relevant literature [76] (see Figure 2 for the pathway of ER and mitochondrial stress caused by hyperlipidemia).

Notably, fatty acid metabolism is cross-linked with inflammatory reaction and oxidative stress via NF-κB, ROS, and PPARs. A series of pathological changes caused by hyperlipidemia are not independent of each other; rather, they have certain interactions.

Protective Effects of Lipid-Lowering Drugs and the Heart (Table 2)

Lipid-Lowering and Anti-Inflammatory Therapy

In a clinical setting, the most commonly employed and effective approach is to reduce the LDL level and simultaneously create a corresponding anti-inflammatory effect. The primary ways to reduce TC are to reduce its absorption and synthesis and promote its degradation. For example, statins can clearly reduce the level of TC and inhibit inflammation. Moreover, the TC transporter NPC1-like1 inhibitor ezetimibe and proprotein-converting enzyme subtilisin 9 (PCSK9) inhibitor are recommended to treat high cholesterol levels [77]. As per the reports of large clinical double-blinded controlled trials, PCSK9 inhibitors significantly reduced the LDL levels of the patients [78].
Several PCSK9 inhibitors have been applied clinically with good outcomes in controlling the blood lipid levels [79]. However, the currently approved PCSK9 inhibitors can only be used as injectables and their price is higher than that of other lipid-lowering drugs. Nevertheless, the good news is that oral PCSK9 inhibitors are currently being developed and tested, which would undoubtedly and significantly improve patient compliance with the prescribed medication [80,81]. As per the TC management guidelines, the roles of lifestyle, niacin derivatives, and cholesteryl ester transfer protein inhibitors in the control of TC have been emphasized [82].

Presently, PPARα agonist fibrate lipid-lowering drugs are widely applied clinically, which not only regulate the metabolic levels of TGs and lipoproteins but also alleviate the inflammatory injury caused by high FFAs [41]. Supplementation with unsaturated fatty acids is an option to reduce triglycerides. Omega-3 is clinically used to lower triglycerides and combat the inflammatory response caused by hyperlipidemia [83]. Similarly, the levels of TGs and FFAs in the body can be reduced through lifestyle interventions or supplementation with nicotinic acid derivatives.

Table 2. Some treatments and main mechanisms.

| Therapeutic mechanism | Medicine or active ingredient | Reference |
|-----------------------|-------------------------------|-----------|
| Lipid-lowering and anti-inflammatory | • Statins | [77] |
| | • Ezetimibe | [77] |
| | • Pcsk9 inhibitor | [78,79] |
| | • Roles of lifestyle | [82] |
| | • Niacin derivatives | [82] |
| | • Cholesteryl ester transfer protein inhibitors | [82] |
| | • Fibrate | [41] |
| | • Coenzyme Q10 | [89,90] |
| | • Omega-3 | [83] |
| Antioxidant | • Resveratrol | [84,85] |
| | • Herba houttuyniae extract | [7] |
| | • Coenzyme Q10 | [86-88] |
| Improving myocardial metabolism | • Trimetazidine | [91-93] |
| | • Ranolazine | [94] |
| | • Piercilin | [97] |
| | • Etomox | [98] |
| | • Pyruvate dehydrogenase kinase inhibitors | [99,100] |
Antioxidant Therapy

In addition, some phytochemicals, such as resveratrol [84,85] and Herba houttuyniae extract [7], have demonstrated their antioxidant capacity in experiments and displayed a protecting role in the myocardium under high-fat conditions. Another plant extract, coenzyme Q10, is an important dietary supplement with cardioprotective effects [86]. Coenzyme Q10 is involved in the oxidative phosphorylation process of the mitochondria, which is an important antioxidant substance with a clear antioxidant role in the disease process [87,88]. Moreover, coenzyme Q10 plays a role in counteracting inflammation [89] and lowering cholesterol [90]. More relevant studies are needed on such phytochemicals before they can be widely applied in clinical practice.

Improvement of Myocardial Metabolism

Trimetazidine, as classical prazosin, plays an important role in mediating myocardial metabolism. It can reduce the uptake of FFAs [91] and strengthen the utilization of glucose by the mitochondria [92], thereby playing a role in protecting the myocardium [93]. As a drug of the same class, ranolazine is effective in improving the myocardial metabolism [94] and in regulating the systemic metabolism in some experiments [95]. Increasing research has demonstrated that ranolazine has a more mechanistic involvement in its antianginal effect [96], but it is not described in detail here.

In addition, some drugs that regulate systemic energy metabolism have also achieved improvement in myocardial metabolism. Piercillin [97] and etomox [98] enhanced glucose utilization in cardiomyocytes by inhibiting carnitine palmitoyl transferase 1, thereby counteracting the adverse effects of lipid accumulation on the myocardial metabolism. Pyruvate dehydrogenase kinase inhibitors have also been demonstrated to enhance myocardial metabolism in the past [99,100]. However, more research is needed in these areas before their clinical application.

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Discussion

The heart acts as an important circulatory organ that can use carbohydrates, fats, and ketones as energy sources [17]. It consumes excessive energy at all times during physiological activities; therefore, the metabolic functions of cardiomyocytes are extremely important for the heart. Excessive lipids can affect heart metabolism and even decrease cardiac functions [10,20]. However, there is no clear definition and diagnostic criteria for “lipotoxic cardiomyopathy” [101]. Fortunately, further studies on ischemic cardiomyopathy, diabetic cardiomyopathy, and heart failure have emphasized the need for research on myocardial metabolic functions. In the future, it will be critical to comprehend the mechanism and pathological changes of hyperlipidemic myocardial injury and provide a theoretical basis for the diagnosis and treatment of the hyperlipidemic myocardial injury.

Conclusions

Hyperlipidemia, as one of the main components of metabolic syndrome, can cause damage to multiple organs [102]. The damage caused by hyperlipidemia to cardiomyocytes and other tissues and organs is mainly caused by an inflammatory reaction, structural and functional changes in the ER and mitochondria, and lipid peroxidation [66]. Presently, considerable achievements have been recorded in controlling blood lipid levels through clinical work [1,102,103]. With the in-depth study of the mechanism of hyperlipidemic myocardial injury, newer methods can be applied to treat myocardial injury and alleviate the cardiac function decline caused by hyperlipidemia, thereby benefiting patients.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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