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PATHOMORPHOLOGICAL FEATURES OF LIVER CHANGES INDUCED BY HYPERCHOLESTEROLEMIA UNDER THE INFLUENCE OF VARIOUS RISK FACTORS

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Abstract

Hypercholesterolemia is one of the major metabolic disorders contributing to the development of structural and functional liver abnormalities. Persistent elevation of serum cholesterol levels disrupts lipid metabolism, leading to excessive cholesterol accumulation within hepatocytes, oxidative stress, inflammatory responses, and progressive hepatic remodeling. The present study aimed to investigate the pathological and morphological characteristics of liver alterations induced by hypercholesterolemia and to evaluate the influence of various risk factors on the severity of these changes. The study analyzed current evidence regarding the mechanisms of cholesterol-induced liver injury, with particular emphasis on hepatocellular degeneration, steatosis, sinusoidal congestion, inflammatory cell infiltration, oxidative stress, activation of hepatic stellate cells, and fibrosis. Particular attention was given to the role of obesity, insulin resistance, aging, high-fat diet, and other metabolic risk factors in accelerating hepatic pathological processes. The findings indicate that hypercholesterolemia causes progressive histopathological alterations characterized by lipid accumulation, mitochondrial dysfunction, inflammatory activation, collagen deposition, and distortion of normal hepatic architecture. The coexistence of additional metabolic risk factors significantly exacerbates liver injury and promotes progression from simple steatosis to fibrosis and cirrhosis. Histopathological examination remains the gold standard for evaluating the severity of hepatic damage and provides valuable information regarding disease progression. Early diagnosis, effective lipid-lowering therapy, antioxidant protection, and modification of lifestyle-related risk factors may substantially reduce hepatic injury and improve clinical outcomes in patients with hypercholesterolemia. These findings emphasize the importance of understanding the pathological mechanisms underlying cholesterol-induced liver damage for the development of effective preventive and therapeutic strategies.

Keywords: hypercholesterolemia; liver pathology; hepatic morphology; steatosis; oxidative stress; fibrosis; hepatocytes; lipid metabolism; risk factors; liver histopathology.

Introduction

Hypercholesterolemia is a widespread metabolic disorder characterized by persistently elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) in the bloodstream. It represents one of the major modifiable risk factors for cardiovascular diseases, including coronary artery disease, ischemic stroke, and peripheral vascular disorders, which remain the leading causes of mortality worldwide (1). Beyond its well-established role in cardiovascular pathology, increasing evidence indicates that hypercholesterolemia exerts profound effects on the liver, the principal organ responsible for maintaining lipid homeostasis, cholesterol synthesis, storage, and excretion.

Continuous exposure of hepatocytes to excessive cholesterol disrupts intracellular lipid metabolism and initiates a cascade of pathological events that gradually impair hepatic structure and function (1).The liver regulates cholesterol balance through coordinated mechanisms involving cholesterol biosynthesis, uptake of circulating lipoproteins, conversion of cholesterol into bile acids, and secretion of lipids into bile. Under physiological conditions, these processes maintain metabolic equilibrium. However, chronic hypercholesterolemia overwhelms these regulatory pathways, resulting in intracellular cholesterol accumulation, mitochondrial dysfunction, endoplasmic reticulum stress, and excessive production of reactive oxygen species. These disturbances contribute to oxidative stress, inflammatory activation, hepatocyte apoptosis, and progressive tissue remodeling (2).

Experimental investigations have demonstrated that prolonged hypercholesterolemia induces a broad spectrum of pathological and morphological alterations in hepatic tissue. These include hepatocellular swelling, fatty degeneration, macrovesicular and microvesicular steatosis, sinusoidal dilatation, vascular congestion, inflammatory cell infiltration, Kupffer cell activation, focal necrosis, and varying degrees of fibrosis (2,3). Histopathological studies further reveal disruption of normal hepatic architecture, degeneration of hepatic cords, collagen deposition within portal tracts, and activation of hepatic stellate cells, all of which contribute to chronic liver injury and impaired hepatic function. These pathological processes may ultimately progress to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and even hepatocellular carcinoma if metabolic abnormalities persist (3).The severity and progression of liver damage associated with hypercholesterolemia are strongly influenced by numerous endogenous and exogenous risk factors. Obesity, insulin resistance, type 2 diabetes mellitus, metabolic syndrome, high-fat diets, aging, sedentary lifestyle, chronic alcohol consumption, smoking, environmental toxicants, and genetic predisposition have all been identified as factors that exacerbate hepatic injury. These conditions amplify oxidative stress and inflammatory signaling pathways through activation of nuclear factor-kappa B (NF-κB), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), transforming growth factor-beta (TGF-β), and other mediators involved in hepatic inflammation and fibrogenesis (3,4). Consequently, simultaneous exposure to hypercholesterolemia and additional metabolic risk factors accelerates structural deterioration of liver tissue and worsens disease prognosis.

Recent advances in molecular pathology have highlighted the importance of oxidative stress, mitochondrial impairment, lipid peroxidation, cytokine imbalance, and apoptosis in the pathogenesis of cholesterol-induced liver injury. Nevertheless, the precise relationship between various risk factors and the extent of pathological alterations within hepatic tissue remains incompletely understood. Comprehensive pathological assessment is therefore essential for identifying early morphological indicators of liver injury, improving diagnostic accuracy, and developing targeted preventive and therapeutic interventions (4).

Considering the increasing global prevalence of hypercholesterolemia and metabolic syndrome, understanding the morphological mechanisms underlying liver damage has become an important objective in experimental and clinical pathology. Evaluation of hepatic histological changes under different pathological conditions may contribute to a better understanding of disease progression and facilitate the development of novel treatment strategies aimed at preventing irreversible hepatic injury.Therefore, the present study aimed to investigate the pathological and morphological characteristics of liver alterations associated with hypercholesterolemia and to evaluate the influence of various risk factors on the development, severity, and progression of these hepatic changes.

Main Part

Hypercholesterolemia induces a wide range of structural and functional abnormalities in the liver through disturbances of lipid metabolism, oxidative stress, inflammatory activation, and progressive tissue remodeling. The liver plays a central role in maintaining cholesterol homeostasis by regulating synthesis, storage, transport, and excretion of cholesterol. When serum cholesterol levels remain

chronically elevated, compensatory mechanisms become insufficient, resulting in intracellular cholesterol accumulation and hepatocellular damage (3).One of the earliest pathological manifestations of hypercholesterolemia is hepatic steatosis. Excessive cholesterol and triglyceride accumulation within hepatocytes causes cytoplasmic lipid vacuolization, cellular enlargement, and displacement of the nucleus toward the cell periphery. Histological examination frequently demonstrates both microvesicular and macrovesicular steatosis, depending on the duration and severity of lipid overload. These changes initially develop without significant fibrosis; however, prolonged exposure to elevated cholesterol levels gradually promotes inflammatory infiltration and extracellular matrix deposition (3,4).

Oxidative stress represents one of the principal mechanisms responsible for cholesterol-induced liver injury. Increased intracellular cholesterol enhances mitochondrial production of reactive oxygen species (ROS), resulting in lipid peroxidation, protein oxidation, DNA damage, and impairment of mitochondrial respiration. These pathological processes reduce cellular energy production and activate multiple intracellular signaling pathways associated with apoptosis and necrosis. Experimental studies have shown that antioxidant defense systems, including superoxide dismutase, catalase, and glutathione peroxidase, become progressively depleted during persistent hypercholesterolemia, thereby aggravating hepatic injury (4).Inflammatory responses further accelerate pathological remodeling of liver tissue. Kupffer cells become activated following exposure to oxidized lipoproteins and damaged hepatocytes, releasing pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β, and interleukin-6. These mediators recruit inflammatory cells into portal and lobular regions, leading to sinusoidal congestion, endothelial dysfunction, and hepatocellular degeneration. Simultaneously, activation of hepatic stellate cells stimulates excessive collagen synthesis, promoting fibrosis and distortion of normal hepatic architecture (5).

Various metabolic and environmental risk factors markedly influence the severity of hepatic lesions associated with hypercholesterolemia. Obesity contributes to increased free fatty acid delivery to the liver, while insulin resistance enhances de novo lipogenesis and suppresses fatty acid oxidation. High-fat diets increase intestinal cholesterol absorption and hepatic lipid accumulation, whereas aging reduces regenerative capacity and antioxidant defense mechanisms. Chronic exposure to environmental toxicants and cigarette smoke further intensifies oxidative stress and inflammatory responses, thereby accelerating progression toward fibrosis (5).Histopathological examination remains the gold standard for evaluating liver injury associated with hypercholesterolemia. Microscopic assessment commonly reveals hepatocyte ballooning, cytoplasmic vacuolar degeneration, inflammatory infiltration surrounding portal tracts, sinusoidal dilatation, vascular congestion, focal necrosis, and progressive collagen deposition. In advanced stages, regenerative nodules and architectural distortion may become evident, indicating transition toward cirrhosis. These pathological findings correlate closely with serum biochemical markers including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), reflecting progressive impairment of hepatocellular integrity (6).

Recent molecular investigations have identified several intracellular signaling pathways involved in cholesterol-induced hepatic injury. Activation of nuclear factor-kappa B (NF-κB) enhances inflammatory gene expression, while transforming growth factor-beta (TGF-β) stimulates hepatic stellate cell proliferation and extracellular matrix production. Moreover, mitochondrial dysfunction activates intrinsic apoptotic pathways mediated by cytochrome c release and caspase activation. Simultaneously, suppression of autophagy reduces cellular capacity to eliminate damaged organelles and lipid droplets, thereby exacerbating hepatocellular degeneration (4,6).Experimental animal models consistently demonstrate that the combination of hypercholesterolemia with additional metabolic risk factors produces substantially greater pathological damage than hypercholesterolemia alone. Animals receiving cholesterol-rich diets together with obesity-inducing regimens exhibit extensive

macrovesicular steatosis, inflammatory infiltration, sinusoidal collapse, and marked fibrosis compared with animals exposed solely to elevated cholesterol. These observations indicate that liver pathology results from the cumulative interaction of multiple pathogenic mechanisms rather than isolated lipid accumulation (5).

Table 1. Major pathological liver alterations associated with hypercholesterolemia under different risk factors

Risk factor	Main pathological alterations	Dominant mechanism	Histopathological findings
Hypercholesterolemia	Hepatic steatosis	Cholesterol accumulation	Macrovesicular and microvesicular steatosis
Obesity	Fatty degeneration	Increased free fatty acid influx	Hepatocyte ballooning and lipid vacuoles
High-fat diet	Lipid overload	Enhanced lipogenesis	Sinusoidal congestion and inflammatory infiltration
Insulin resistance	Metabolic dysfunction	Reduced β-oxidation	Hepatocyte degeneration and focal necrosis
Oxidative stress	Cellular injury	ROS overproduction	Lipid peroxidation and apoptosis
Aging	Reduced regeneration	Mitochondrial dysfunction	Fibrosis and architectural distortion

The severity of these pathological changes generally increases according to the duration of hypercholesterolemia and the coexistence of additional metabolic disorders. Consequently, early identification and modification of these risk factors may significantly reduce progression toward irreversible liver fibrosis and chronic liver disease (6).

The progression of liver injury during hypercholesterolemia is determined not only by excessive lipid deposition but also by the interaction between metabolic imbalance, oxidative stress, chronic inflammation, and cellular remodeling. These mechanisms operate simultaneously and gradually transform reversible hepatic alterations into irreversible pathological lesions. Consequently, the severity of histopathological changes depends on both the duration of hypercholesterolemia and the presence of additional risk factors such as obesity, insulin resistance, aging, and consumption of high-fat diets (3).Microscopic evaluation of liver tissue obtained from experimental models of hypercholesterolemia consistently demonstrates progressive disruption of normal hepatic architecture. During the early stage, hepatocytes exhibit cytoplasmic swelling accompanied by small lipid vacuoles surrounding the nucleus. This phenomenon reflects intracellular cholesterol accumulation resulting from impaired lipid metabolism. As cholesterol concentration increases, hepatocytes enlarge, the cytoplasm becomes vacuolated, and nuclei are displaced toward the periphery, producing the characteristic appearance of macrovesicular steatosis. Sinusoidal spaces gradually become compressed due to hepatocyte enlargement, leading to impaired hepatic microcirculation and localized tissue hypoxia (3,4).

Persistent hypercholesterolemia also affects hepatic vascular structures. Congestion of central veins and portal vessels becomes increasingly evident as lipid accumulation progresses. Endothelial dysfunction decreases sinusoidal blood flow, promotes leukocyte adhesion, and facilitates migration of inflammatory cells into hepatic lobules. Histological sections frequently reveal dilation of hepatic sinusoids, erythrocyte aggregation, and focal hemorrhage in severely affected regions. These vascular alterations reduce oxygen delivery to hepatocytes, thereby accelerating cellular degeneration and

necrosis (4).Inflammatory infiltration represents another important morphological feature of cholesterol-induced liver injury. Activated Kupffer cells recognize oxidized low-density lipoproteins and damaged hepatocytes through pattern-recognition receptors, leading to production of tumor necrosis factor-alpha, interleukin-1β, interleukin-6, and numerous chemokines. These mediators recruit macrophages, neutrophils, and lymphocytes into portal tracts and hepatic lobules, producing chronic inflammatory reactions that amplify tissue destruction. Histopathological examination commonly demonstrates diffuse inflammatory infiltration surrounding portal triads together with degeneration of adjacent hepatocytes (5).

Oxidative stress further intensifies hepatic injury through excessive production of reactive oxygen species. Lipid peroxidation damages phospholipid membranes, increases cellular permeability, and disrupts mitochondrial function. Ultrastructural studies have demonstrated swollen mitochondria, fragmented cristae, dilated endoplasmic reticulum, and lysosomal activation in hepatocytes exposed to prolonged hypercholesterolemia. These abnormalities impair ATP synthesis and activate apoptotic pathways through mitochondrial release of cytochrome c and subsequent activation of caspase enzymes (4,5).Another characteristic pathological feature is progressive activation of hepatic stellate cells. Under physiological conditions these cells remain quiescent and store vitamin A within the space of Disse. During hypercholesterolemia, inflammatory cytokines and transforming growth factor-beta stimulate stellate-cell activation and transformation into collagen-producing myofibroblasts. Consequently, excessive extracellular matrix proteins accumulate within portal areas and hepatic lobules, producing periportal and perisinusoidal fibrosis. Continued collagen deposition disrupts hepatic architecture, impairs sinusoidal exchange, and contributes to declining liver function (5,6).

Comparative investigations indicate that animals exposed to hypercholesterolemia together with obesity or diabetes develop substantially more severe pathological alterations than animals with isolated hypercholesterolemia. Combined metabolic disturbances increase hepatic triglyceride accumulation, intensify oxidative injury, and prolong inflammatory activation. Histological examination frequently reveals diffuse macrovesicular steatosis involving more than 60% of hepatocytes, widespread inflammatory infiltration, bridging fibrosis, and focal areas of hepatocellular necrosis. These findings suggest that multiple metabolic risk factors act synergistically to accelerate disease progression (6).

Table 2. Histopathological progression of liver injury during hypercholesterolemia

Stage	Microscopic characteristics	Predominant mechanism	Clinical significance
Early stage	Mild hepatocyte swelling, microvesicular steatosis	Intracellular cholesterol accumulation	Usually reversible
Intermediate stage	Macrovesicular steatosis, sinusoidal congestion, inflammatory infiltration	Oxidative stress and cytokine activation	Progressive liver dysfunction
Advanced stage	Ballooning degeneration, focal necrosis, collagen deposition	Stellate-cell activation and fibrosis	Chronic liver injury
Late stage	Bridging fibrosis, architectural distortion, regenerative nodules	Persistent inflammation and extracellular matrix accumulation	Cirrhosis and hepatic insufficiency

Morphometric analysis performed in numerous experimental studies has demonstrated a positive correlation between serum cholesterol concentration and the severity of hepatic lesions. Elevation of total cholesterol and LDL-C is associated with increased steatosis scores, inflammatory activity,

collagen deposition, and fibrosis stage. Simultaneously, serum biochemical markers such as ALT, AST, ALP, and GGT increase progressively, reflecting hepatocellular membrane damage and impaired liver function. These biochemical alterations strongly correlate with histopathological findings and may therefore serve as useful indicators of disease progression (6).

Recent molecular studies have further demonstrated that suppression of antioxidant defense systems, activation of NF-κB signaling, increased expression of transforming growth factor-beta, and dysregulation of mitochondrial metabolism collectively determine the extent of pathological liver remodeling. Therefore, prevention of oxidative stress together with correction of dyslipidemia may represent effective strategies for limiting hepatic injury associated with hypercholesterolemia. Early intervention aimed at controlling cholesterol levels and reducing additional metabolic risk factors is expected to preserve normal hepatic architecture, decrease inflammatory activity, and prevent progression toward irreversible fibrosis and cirrhosis (6).

Conclusion

Hypercholesterolemia is a major metabolic disorder that significantly contributes to the development of pathological and morphological alterations in the liver. Persistent elevation of serum cholesterol disrupts lipid homeostasis, resulting in hepatocellular lipid accumulation, oxidative stress, inflammatory activation, mitochondrial dysfunction, and progressive fibrosis. These pathological mechanisms collectively impair hepatic architecture and functional capacity.The severity of liver injury is markedly influenced by various endogenous and exogenous risk factors, including obesity, insulin resistance, aging, high-fat diets, and chronic oxidative stress. The coexistence of these factors accelerates hepatocyte degeneration, inflammatory infiltration, sinusoidal congestion, collagen deposition, and activation of hepatic stellate cells, thereby promoting the progression from simple steatosis to fibrosis and potentially cirrhosis.Histopathological evaluation remains the most reliable approach for assessing the extent of liver damage associated with hypercholesterolemia. Morphological examination provides valuable information regarding disease progression and correlates closely with biochemical markers of hepatic injury. Early diagnosis, effective lipid-lowering therapy, antioxidant protection, lifestyle modification, and elimination of modifiable risk factors may substantially reduce hepatic damage and prevent irreversible structural changes.Further experimental and clinical investigations are required to clarify the molecular mechanisms underlying cholesterol-induced liver injury and to identify novel therapeutic targets capable of preventing disease progression. Comprehensive understanding of these pathological processes will contribute to improving the prevention, diagnosis, and treatment of liver disorders associated with hypercholesterolemia.

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