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NEGATIVE EFFECTS OF HYPERLIPIDEMIA ON HUMAN HEALTH

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Abstract
A diet rich in fat increases the risk of many diseases, which are the leading cause of death in adults. Whenever the higher the percentage of body fat, the higher the risk of cardiovascular disease. In view of the severe damage that affects human health when the level of fat is high, the current review aimed to investigate the negative effects of excessive fat on human health, by reviewing the mechanisms of excessive fat, its complications and methods of treatment, A review of the lipid profile was presented through the definition of cholesterol and lipoproteins of cholesterol, which included Low density lipoproteins (LDL-C), High density lipoprotein cholesterol (HDL-C), and very low density lipoproteins. Very low density lipoproteins (VLDL-C) as well as triglycerides (TG).
The role of excess fat on inducing atherosclerosis was discussed, and the relationship between high body fat and the level of adipose tissue hormones, which included leptin and resistin, was presented. The current review indicated the role of the enzyme HMG-CoA reductase in the processes of manufacturing cholesterol in vivo. Finally, the side effects of hyperlipidemia on human health were presented, which included the negative effects of hyperlipidemia on the lipid profile, the concentration of the hormone resistin, the concentration of leptin, oxidative stress variables and the activity of liver enzymes, in addition to the negative effects of hyperlipidemia on the histological parameters of the liver and aorta.

Key words: Hyperlipidemia, Atherosclerosis, Leptin , Resistin, Oxidative Stress, Liver, Aorta.

Introduction

Hyperlipidemia is a very important risk factor for predicting atherosclerosis, coronary artery diseases and cerebral vascular diseases, which are the leading cause of death in the world (Zhang *et al*., 2018). Hyperlipidemia is characterized by elevated Total Cholesterol (TC) and Low Density Lipoprotein Cholesterol (LDL-C) and decrease High Density Lipoprotein Cholesterol levels (HDL-C) in the blood serum, and that the hyperlipidemia associated with lipid disorders Dyslipidemia is the cause of

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cardiovascular diseases arising from atherosclerosis and disturbance of the oxidative stress balance state in the body (Ahmed *et al*., 2020; Ahmed *et al*., 2022a). Atherosclerosis is a common disease of the network of arteries and is known as a progressive disease and a silent killer that narrows the large and medium-sized coronary arteries, reduces blood flow to the heart muscle and gives rise to the so-called coronary artery diseases (Ahmed *et al*., 2022b).

Hyperlipidemia is caused by disturbances in lipid metabolism including elevated levels of TC, TG and LDL-C, or by low levels of HDL-C that negatively affect cholesterol transport pathways (Surya *et al*., 2017). Dietary intake may not be the main source of cholesterol as 80% of it is built up in the body, but dietary intake affects the amount of total cholesterol to some extent (Ahn *et al*.,2017). A bad or unhealthy diet, mainly when eating foods rich in fat, is a risk factor, in addition to other factors such as being overweight, smoking, excessive alcohol consumption, lack of physical activity and lack of exercise, as well as the incidence of some diseases such as diabetes, kidney disease, pregnancy and endocrine disease (Varghese *et al*., 2017).

Hyperlipidemia

Also known as hyperlipidemia, it is a major risk factor for atherosclerosis, coronary heart disease, cardiac arrest, and renal failure, and recently it has become a major health problem in the world. It is believed that cardiovascular diseases are the leading cause of death in the world (Jorgensen *et al*., 2013). Getting rid of stored fat in the body helps reduce body weight and improves insulin sensitivity, thus reducing blood glucose levels and avoiding diabetes, as hyperlipidemia is a heterogeneous group of disorders characterized by an excess of fat in the bloodstream, and hyperlipidemia is also known as an increase in one or more plasma lipids, including triglycerides, cholesterol, cholesterol esters, and phospholipids (Miao *et al*., 2016; Ahmed *et al*., 2022c), It is a condition characterized by high cholesterol levels, also called hypercholesterolemia. Hyperlipidemia occurs due to a defect in lipoproteins due to an increase or decrease in its production, thus causing an increase in the levels of LDL-C, which is the most common, and the reason for this is an increase in TC and the level of TG with a decrease in the levels of HDL-C and an increase in body mass index (wakea *et al*.,2019).

This disease is divided into two types, the first type is primary hyperlipidemia, and this type usually occurs as a result of genetic problems such as a mutation within the receptor protein, and may result from a defect in one or several genes as a result of a change in diet and lack of appropriate sports activities. As for the second type, it is secondary hyperlipidemia. This type occurs due to diseases such as diabetes, chronic nephrotic syndrome, alcoholism, use of drugs such as corticosteroids and others (Shukr *et al*., 2019). It is considered one of the most important risk factors for cardiovascular diseases, as venous hypertension accounts for a third of all deaths worldwide, and researchers expect that deaths due to cardiovascular diseases will increase from 17.3 million cases annually at the present time to 23.6 million deaths by 2030 (Verma, 2016). There may be significant differences in the levels of the prevalence of hyperlipidemia between different ethnic groups, and that different dietary habits, lifestyle, physical activity, increased gender and age factors, as well as genetic origin play a role in the

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prevalence of hyperlipidemia, as high cholesterol was recorded as the person advanced in age (Ruixing *et al*., 2006; Grauvogel *et al*., 2010).

Complication of Hyperlipidemia

Lipid metabolism disorders are pathological disorders in which problems occur in the breakdown or synthesis of fats. Disorders of lipid metabolism are associated with increased concentrations of plasma lipids in the blood such as LDL-C, TG and VLDL-C that often lead to cardiovascular disease (Gyton and Hall, 2020).

The cause of hyperlipidemia is due to two possible processes, the first is the excessive production of VLDL-C by the liver as a result of the increased flow of free fatty acids to this organ, and the second process is a defect in the process of decomposition of VLDL-C and TG and Chylomicrons by lipoprotein lipase enzyme secreted by the liver. When there is a decrease or defect in the levels of this enzyme, it is not possible to analyze TGs, as well as the metabolism of VLDL-C and Chylomicrons may occur (Jap *et al*., 2003).

Hyperlipidemia is characterized by the accumulation of triglycerols within the liver cells, and the condition can progress to more serious liver diseases, such as non-alcoholic steatohepatitis, liver fibrosis, and cirrhosis, rarely, it causes liver carcinoma (Kleiner *et al*., 2005). Previous studies have shown that feeding mice a high-fat diet stimulates liver degeneration and fibrosis, the first step in inducing hyperlipidemia (Cano *et al*., 2009).

Among the most important complications caused by hyperlipidemia are: First: Coronary artery disease (CAD) The main cause of coronary artery disease is excess fat, as it causes the accumulation of fat and the formation of fibrous plaques in the arterial walls, which causes narrowing in the arteries that supply blood to the heart muscle, thus limiting blood flow and stopping the oxygen needs of the heart from being met (Gao *et al*., 2012). Second: - Myocardial infarction (MI) This condition occurs when blood or oxygen is prevented from flowing in the arteries of the heart, causing heart cells to die or become damaged. Or, the cause may be a breakdown in arterial plaques. Recent studies have shown that about a quarter of myocardial infarction survivors are people with hyperlipidemia (Zodda *et al*., 2018). Third: Retinal vein occlusion (RVO) This disease is associated with people who have a high level of cholesterol, a condition that causes blockage of blood drainage from the retina, leading to vision loss, and it was found that people who have a high level of cholesterol are in 2.5 times the risk of retinal obstruction (Ganesan *et al*., 2018). Fourth: - Ischemic stroke is a major cause of death and occurs due to blockage of the artery by a blood clot that disintegrates in a small vessel and thus closes the small blood vessels inside the brain. Studies have shown that a decrease in LDL-C and TC by 15% clearly reduces the risk of heart attack. (Amarenoco and Labreuche, 2009; Welde, 2017).

Treatment of Hyperlipidemia

1. Change in therapeutic lifestyle: Modifying the diet as well as regular physical activity is one of the most important reasons for treatment, such as quitting smoking and reducing weight, and this treatment is effective in the beginning, especially in mild cases of hyperlipidemia in healthy people from

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coronary artery disease and when A person follows a healthy diet that should reduce cholesterol intake (Armstrong, 2013).

2. Treatment with lipid-lowering drugs: The beginning of treatment is to change the daily lifestyle of food, movement and exercise. If these changes do not affect the treatment, the treatment is through medicines, and there are many medicines that are used at the present time to treat hyperlipidemia, including statins, fibrates, and Niacin , Bile acid sequestrants (Logue *et al*., 2015).

Lipid Profile

Fats are organic substances that are soluble in organic solvents, but do not dissolve in water, and of the polar derivatives, they have two groups, one of them is polar, hydrophilic and the other is non-polar, hydrophobic (Akoh, 2017). Fats in the bloodstream are usually classified as triglycerides and cholesterol (Braamskamp *et al*. .,2012). And fats are necessary for many of the normal functions of living organisms, and are important components of the membranes of living cells, and are used to store energy, and can act as an aid to enzymes and the manufacture of hormones (Karam *et al*., 2017).

Cholesterol

It is a soft and waxy substance that is one of the natural components of fats in the blood and all cells of the body. Cholesterol is an essential part of a healthy body, but it has great risks when its level in the blood increases, as it causes cardiovascular diseases that lead to stroke or cardiac arrest. Likewise, the presence of large amounts of it in the blood causes the emergence and development of plaques on the walls of the arteries, which causes the closure of the bloodstream and prevents it from reaching the brain, heart and other organs. A large part of it is made inside the cells of the body and through the manufacture of bile acids, sex hormones, and vitamin D3 (Lyu *et al*., 2019). There are two sources through which cholesterol is manufactured in the body. They are an internal source, which is made inside the liver, and an external source is through eating animal products such as dairy and meat such as liver, as well as eggs and fish liver oil (Guo *et al*., 2018). The liver has an important role in cholesterol metabolism because it contains low-density lipoprotein receptors, and it also has a major role in the formation of the bulk of cholesterol of endogenous origin (Goto, 2002).

Cholesterol Lipoproteins:

Low Density Lipoproteins Cholesterol (LDL-C)

They are very small particles found in the bloodstream that transport cholesterol from the liver to the body tissues to be stored (Black, 2007). It is also known as bad cholesterol because of its high content in the blood, and it is the important line in the development of heart diseases, including atherosclerosis, and works on the fragmentation and destruction of the VLDL-C molecule and its association with cholesterol and protein (Walker *et al*., 2013), and it was found that its percentage in males is higher than in Females, as it is estimated at (40-50%) of total plasma proteins, and it has a significant role in the risk of coronary heart disease (Tierney *et al*., 2005).

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High Density Lipoprotein Cholesterol (HDL-C)

It is one of the smallest types of lipoproteins, but it is the most dense, consisting of 50% protein, 18% cholesterol, and very small amounts of TG (Racette *et al.*, 2015). This type of protein is characterized by having antioxidant properties, as well as being anti-inflammatory, as it has a negative relationship with heart disease, and is believed to be able to absorb cholesterol crystals that have begun to be deposited on the walls of the arteries, as it helps to avoid atherosclerosis (Ridgway and Mcleod, 2016) . Recent studies have shown that when the HDL-C ratio decreases, the incidence of heart diseases increases, and it was found that in women, it is in greater proportions than in men, and its danger increases when the age is over 65 years (Tierny *et al.*, 2006; Guyton and Hall, 2020).

Very Low Density Lipoproteins Cholesterol (VLDL-C)

It is made mainly in the liver, but also made in the intestine from triglycerides and cholesterol, which is responsible for transporting phospholipids, triglycerides, and cholesterol esters of endogenous origin. It was found that this type of lipoproteins increases in heart disease (Ridgway and Mcleod, 2016), because the molecules of this protein carry triglycerides in the circulatory system and also transfer fats made in the liver to other body tissues (Lin *et al.*, 2016).

Triglycerides (TG)

It is one of the most common types of fats, and it is a group of cholesterol esters with triple fatty acids. It has several functions in the body of the organism, as it prepares cells with energy, as a large amount of fatty acids present in the plasma are stored through esters linked with cholesterol within fatty tissues. , as the concentration of glycerides is balanced at all times according to the rate of their entry into the cells and their re-removal, and the change in concentration depends on these two factors (Kaplan *et al.*, 2011). Triglycerides (TG) cause heart disease, including atherosclerosis, high blood pressure, and heart disease (Mehta *et al.*, 2002). In cases of oxidative stress, the increase in free radicals causes a decrease in the enzyme lipoprotein lipase present in different tissues of the body, and thus this decrease causes an imbalance in lipid levels and an increase in the concentration of TG in the blood (Stohsj *et al.*, 2000).

Atherosclerosis

Coronary heart disease due to atherosclerosis is one of the most common cardiovascular diseases in the population, especially in adults aged 40 years and over (Chuang *et al.*, 2016). Atherosclerosis is an inflammatory vascular disease that clinically affects all blood vessels, including cerebral, coronary and peripheral vessels (Clemmons, 2015; Lepedda and Formato, 2020). Atherosclerosis results from the deposition of fats in the inner walls of the blood vessels, so that they grow to the point of obstructing blood flow, and these deposits clump together, which leads to the narrowing of the artery and the formation of a clot or thrombus, causing a stroke (Pownall *et al.*, 2015).

The disease develops over many years in the inner layer of large and medium-sized arteries, with devastating manifestations, usually after the fourth or fifth decade, and that the main contributor to the progression of the disease is abnormalities in the metabolism of lipids and lipoproteins due to the

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presence of high concentrations of cholesterol levels in plasma, especially LDL-C and cholesterol in the blood (Sato *et al.*, 2002). The causes of atherosclerosis are multiple, the most important of which is hyperlipidemia, especially if it is accompanied by hyperglycemia as a result of increased oxidative stress. Oxidative stress is an integral part of the mechanism of development of cardiovascular diseases and atherosclerosis. Clinical and epidemiological studies have confirmed that high blood pressure has a stronger effect than other risk factors such as smoking, alcohol, age and lipoprotein levels, and causes fibrosis and enlargement of blood vessels and small arteries (kirabo *et al.*, 2014).

Atherosclerosis Mechanism

It is the process of forming atherosclerotic plaques in the inner layer of the arteries, it gradually develops with the development of inflammation and the accumulation of fat in a large way, especially LDL-C. Arteritis is the first stage of the disease, as it begins with a qualitative change in the inner arterial surface (Libby *et al.*, 2013). There are three layers of tissue in a normal artery: the inner layer (endothelium), the middle layer, and the outer layer (Tabas *et al.*, 2007). Endothelial cells possess adhesion molecules that at the beginning of the first stage of sclerosis capture leukocytes on their surface when affected by irritating stimuli, and then lead to their migration to the inner layer. When plaques form under the endothelium, due to changes in endothelial permeability, LDL-C molecules help migrate into the arterial wall (Fig. 1). White blood cells within the inner layer mature into macrophages that take in LDL-C molecules, and endothelial dysfunction can be caused by inflammatory cytokines, oxidative stress, hypertension, hypercholesterolemia, and diabetes mellitus (Tabas, 2010; Gimbrone and Garcia, 2016).

The body's immune system responds to the damage done to the artery walls from oxidation of these molecules by sending monocytes to the site of injury to devour them (Kaplan and jaskson, 2011). Under oxidative stress, LDL-C is transformed into oxidative lipoproteins OX-LDL and is devoured by Macrophage, stimulating endothelial cells to produce cytokines, chemokines (Ramji and Davies, 2015). The macrophages are unable to eat them and fuse with them to form foam cells. The macrophages take the form of a lipoprotein and then go through apoptosis, which ends with the accumulation of large amounts of cellular waste and cholesterol, which ends with the formation of an area of cellular degeneration with the accumulation of fats in the layers of the arteries. In the advanced stages, smooth muscle cells migrate from the outer layer of the artery to the inner layer, causing increased secretion of collagen and forming fibrous plugs in the artery lining called plaques. Atherosclerosis is not limited to the heart arteries, but can also occur in other areas of the body, such as the brain (Hauser *et al.*, 2011).

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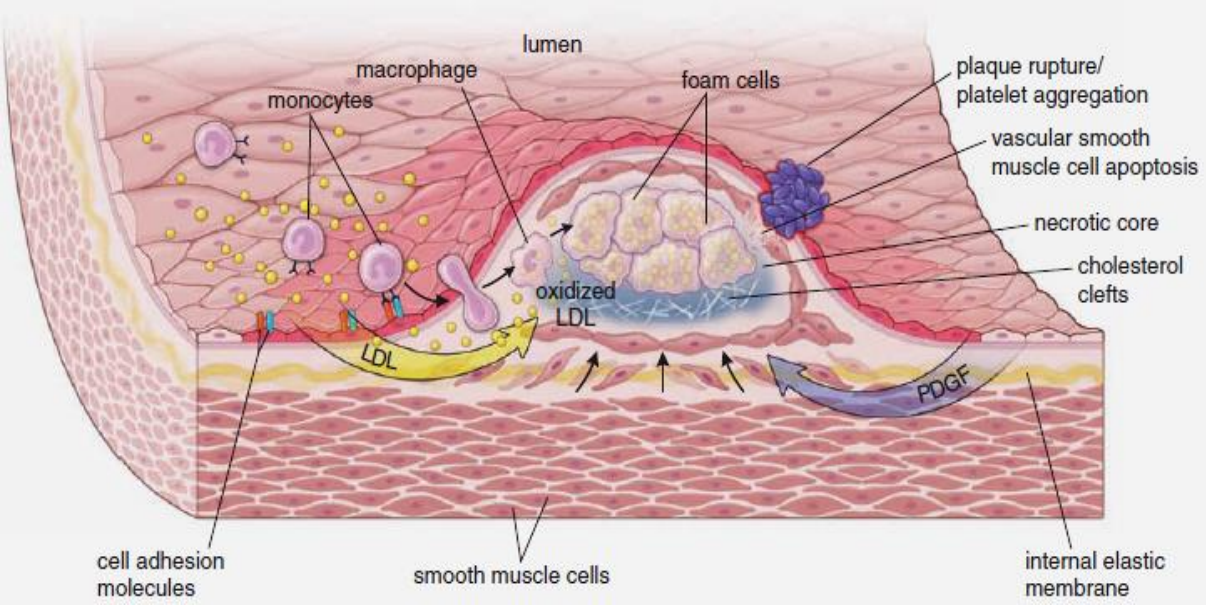

Figure 1. A schematic diagram of the cellular interactions of atherosclerosis (Pawlina and Ross, 2016).

Adipose Tissue Hormones

Leptin Hormone

It is a protein with a molecular weight of 16 KD. It contains 167 amino acids. It is one of the most important hormones derived from adipose tissue. It has a very important role in regulating energy within the body as well as regulating body weight (Alsamadi *et al.*, 2014). White adipose tissue is the important source of leptin, but it is also produced from other tissues such as brown adipose tissue, placenta, ovaries, skeletal muscle, Stomach, as well as bone marrow (Margetic *et al.*, 2002). Research has shown that leptin has a significant role in regulating body mass and sharp changes in the energy balance associated with appetite, as a deficiency of the hormone can cause obesity (Allison *et al.*, 2013). In addition, the hormone has a role in fertility and childbearing, as it was found that very skinny women with small amounts of fat suffer from menstrual disorders, and that the injection of this hormone into laboratory animals affects the secretion of the hypothalamus gland, as it increases the secretion of the gonadotropin-inducing hormone, which in turn stimulates the pituitary gland In the secretion of LH and FSH for their essential role in the fertilization process in males and females (Ahima *et al.*, 2000). The hormone has a relationship with obesity and heart disease, as the increase in the hormone increases the incidence of myocardial infarction, because the increase in the level of the hormone is associated with an increased risk of disease (Diab, 2005). The leptin hormone is an indicator of some heart diseases, and it was found (Wang *et al.*, 2014) that the hormone has a role in the development of atherosclerosis. The hormone affects the blood lipids. When the hormone rises, it is accompanied by a high level of triglycerides, with high TC and LDL-C, with a low level of HDL-C in both sexes. In addition, it increases the burning of fat in the muscles and reduces the production of VLDL-C in the liver (Lundasen *et al.*, 2003).

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The Relationship Between Hyperlipidemia and Leptin Concentration

Leptin is secreted from adipose tissue, hypothalamus, stomach, placenta, skeletal muscle, and mammary epithelial cells. It is considered one of the hormones that signal the brain to feel full and regulate nutrition and energy in the body by regulating the secretion of hormones that increase appetite. It works by the feedback mechanism (Gale *et al*., 2004 ; Norman *et al*., 2015). A positive relationship was found between the hormone leptin and the hormone insulin, and a negative relationship between leptin and glucose levels in the blood, and that increased insulin secretion increases the formation of leptin messenger ribonucleic acid (mRNA) in adipose tissue. In 2002, researchers were able to use leptin in the treatment of diabetes when they found that it reduces insulin resistance and prevents the accumulation of fat in the body (Miyanaga *et al*., 2003), and leptin plays an important role in regulating body weight, metabolism and energy (Alsmadi *et al*., 2014), It was found that subcutaneous injection of leptin in subjects with congenital leptin deficiency reduces TC, TG and LDL-C , while increasing the concentration of HDL-C in adipose tissue (GM *et al*., 2002).

Resistin Hormone

Resistin was originally discovered in mice in 2001 and has been named for its ability to resist insulin (Steppan *et al*., 2001). It has been suggested as a link between obesity and diabetes. The hormone resistin modulates molecular pathways associated with metabolic, inflammatory and autoimmune diseases, as well as cardiovascular disease. Recent studies indicate that resistin directly causes endothelial cell dysfunction. Clinical studies have indicated that resistin is a predictive factor for coronary artery disease and cardiovascular disease mortality. Furthermore, the hormone appears to be involved in angiogenesis, thrombosis, and vascular smooth muscle cell (VSMC) migration and proliferation, all of which contribute to atherosclerosis (Calabro *et al*., 2004).

Resistin hormone is a peptide that ends with the amino acid Cystein, its molecular weight is 12.5 KD, and it is a class of cysteine-rich proteins and is secreted from adipose tissue and the macrophages in it. There are three forms of monomer, trimer, and hexmer, and the smaller molecule is the most effective. The hormone receptor is located on the surfaces of adipose tissue-producing cells and is known as decorin. The clinical importance of this hormone is due to the association of its levels in the serum with the increase in Arteriosclerosis cardio vascular disease, which makes it a linking factor between obesity and the development of cardiovascular disease in obese people (Janke *et al*., 2002). Resistin is involved in the primary physiological processes of atherosclerosis in arterial walls. It promotes endothelial dysfunction, smooth muscle cell migration and proliferation, monocyte activation and proliferation, and macrophage to lipid-filled foam cells that compose the major cellular component of the fatty filaments characteristic of Atherosclerotic plaques (Jamaluddin *et al*., 2012).

The Relationship Between Hyperlipidemia and Resistin Concentration

Resistin is a peptide hormone secreted from fat cells of rodents, and it is one of the proteins rich in the amino acid cysteine (Steppan *et al*., 2001). The researcher (Bokarewa *et al*., 2005) noted the possibility

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of a relationship between resistin and cardiovascular disease, which indicates the possibility of a possible link between resistin and cardiovascular disease through inflammatory pathways.
The elevated resistin level upon induction of hyperlipidemia is consistent with its effect on endothelial function and vascular smooth muscle cell migration, which are major pathophysiological mechanisms of atherosclerosis. Moreover, recitin has been observed to play a vital role in increasing the level of very low-density lipoprotein and low-density lipoprotein in the obese person causing direct atherosclerosis (Rizkalla *et al*., 2009).
The hormone resistin had a clear role as one of the indicators of heart disease, especially cardiovascular disease and heart failure. In rabbits, the expression of the resistin gene is increased in the atherosclerotic plaques, which increases the macrophage and lipid content of the sclerotic plaques. Because of these effects, it not only increases the size and progression of atherosclerotic plaque, but also increases its instability, stability, and susceptibility to injury, because it activates the endothelial cells of the blood vessels and stimulates the proliferation of smooth muscle cells, thus increasing the thickness of the lining of the coronary arteries (Rashid, 2013).

HMG-CoA reductase Enzyme

Creates more than two-thirds of cholesterol produced in the liver (William et al., 2002), and the enzyme HMG-COA reductase controls the rate of cholesterol synthesis in the liver through the mevalonate pathway, which stimulates the conversion of HMG-COA to mevalonate (kopple and massry, 2012). The liver is the main organ in the process of controlling and regulating cholesterol levels in the body.
In mammals, the concentration of cholesterol inside cells is regulated by the endogenous structure and the intake from the outside (through diet), and the endogenous synthesis takes place through feedback by the enzyme Hepatic HMG-COA reductase, while the external source is controlled by the LDL-C receptors by a mechanism Enzyme and LDL-C receptor feedback is mediated by genetic regulation (Maron *et al*., 2000).

The Negative Effects of Hyperlipidemia on The Lipid Profile

An increase in the concentration of TC, TG, LDL-C, VLDL-C, and a decrease in HDL-C expresses a state of dyslipidemia or hyperlipidemia. These disorders are caused by several factors that have a role in the process of fat metabolism, including the disruption in the processes of fat absorption and excretion (Ahmed *et al*., 2020). In addition, the rise in lipid variables may be due to the excessive production of free radicals and the depletion of antioxidants, which may cause oxidative damage to hepatocytes and thus disrupt the normal lipid metabolism function as a result of inhibiting the enzymes responsible for these mechanisms (Mazmancı *et al*., 2011). Scientific research has indicated that the state of oxidative stress leads to imbalances in fatty acid metabolism and the emergence of lipid peroxidation, and thus the accumulation of fat in the blood serum and liver tissue, which may cause non-alcoholic fatty liver disorder (Lankarani *et al*., 2013).
LDL-C is responsible for transporting TC to the cells of the body, it transports about 60-70% of the TC , so the increase in TC levels is followed by an increase in LDL-C that cannot be eliminated in the process

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of fat metabolism, and most likely will enter the space under The endothelial prelude to oxidation carries oxidized LDL-C mediated by macrophage inhibitors, the lipid-laden macrophages are foam cells that will leave a pulp rich or full of lipids and cholesterol after storage and then start atherosclerosis (Beckman *et al.*, 1990). As the oxidation of these fats turns them into smaller, oxidized LDL-C particles, which gives them the opportunity to move and enter the tissues of blood vessels, especially arteries and deposition in them, causing the development of atherosclerotic lesions, which is one of the main risk factors for cardiovascular diseases (Zheng *et al.*, 2018; Elkhateeb *et al.*, 2019).

The researcher (Abu-Raghif *et al.*, 2015) found that causing hyperlipidemia in white mice by feeding them on a high fat diet causes an imbalance in the level of fat represented by an increase in the concentration of TCl, TG, LDL-C and VLDL-C with a decrease in the level of fat. On the other hand, the researcher also found a disturbance in the case of oxidative stress, represented by a high concentration of MDA and a decrease in GSH concentrations, and he indicated that the change in oxidative stress factors may be due to the deposition of fat in the liver, which in turn leads to a defect in the function of hepatocytes and their role in regulating fat metabolism. The researchers (Al-Razzak Abdu Al-Latif and Faisal Jaber, 2013) also found that inducing hyperlipidemia in rabbits led to an increase in MDA concentration and at the same time, a decrease in GSH concentration compared to the control group. The oxidative stress disorder causes the formation of damaged areas in the epithelium of blood vessels, an increase in its permeability, a decrease in its elasticity, and the development of atherosclerosis. Several studies have confirmed that people who have high levels of lipids and lipoproteins have a high predisposition to atherosclerosis. The reason for the high levels of atherosclerosis evidence may be attributed to the increased production of free radicals that break down and remove nitric oxide, NO, which has anti-atherogenic properties, as well as damage to the lining of the arteries, which stimulates phagocytes to produce large amounts of free radicals that oxidize fats, especially LDL-C was enhanced by an increased risk of atherosclerosis (Stevinkel *et al.*, 2004).

The Negative Effects of Hyperlipidemia on The Oxidative Balance

Hyperlipidemia leads to a decrease in the level of antioxidants and a high level of free radicals, and thus free radicals attack the unsaturated fats that enter the composition of cell membranes, causing fat super-oxidation, or lipid peroxidation and the production of malondialdehyde(MDA) as a final product of this process. The MDA is the most widely used indicator in detecting the lipid peroxidation and it is a measure of the generation of free radicals, and its high concentration in animals indicates that hypercholesterolemia that enhances the lipid peroxidation (Prasanna and Purnima, 2011; Ahmed *et al.*, 2021). The lipid peroxidation is initiated by the free radical attack on the unsaturated fatty acids in the membrane, which leads to their conversion and fragmentation into reactive alkanes and aldehydes (Olorunnisola *et al.*, 2012).

The continuous production of cholesterol increases the production of free radicals in several ways. It increases the activity of the enzyme systems that produce the three main oxidation: such as the enzyme myeloperoxidase, which is produced by neutrophils and monocytes and produces toxic hypochlorous acid, and the enzyme Xanthine Oxidase and NADPH Oxidase, as the latter works to transfer the electron

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to the oxygen molecule , and the superoxide eventually forms hydrogen peroxide. Increased lipid peroxidation inactivates antioxidant enzymes by cross-linking with MDA and this will cause an increase in the accumulation of superoxide, hydrogen peroxide and hydroxyl radical, which can increase lipid super-oxidation (Noeman *et al*., 2011).

Negative Effects of Hyperlipidemia on The Liver

Disorders in blood lipids, represented by an increase in the concentration of most lipid variables, especially cholesterol, when induced hyperlipidemia, and the accompanying imbalance in oxidative stress variables, increase the levels of free radicals and active oxygen species, causing oxidative damage to liver cells, which often leads to greater oxidation of liver fat as a result of activation of Kupffer cells, which causes the emergence and maintenance of the inflammatory response and the development of fibrosis (Jun Luo *et al*., 2015). The results of the study (Ahmed *et al*., 2022a) when hyperlipidemia was stimulated in rats and the examination of histological sections of the liver showed histological disorders that included the presence of deposition of fatty droplets and their accumulation in hepatocytes with the presence of vacuolar degeneration and congestion of the central veins of the liver with the presence of fibrosis and the researcher attributed the reason for this to an increase free radical levels in hepatocytes causing various histological lesions in the liver.

Oxidation is an essential biological process for many living organisms to produce energy. However, the uncontrolled production of oxygen-derived free radicals contributes to the emergence of many diseases, such as cancer, rheumatoid arthritis, and atherosclerosis, as well as to the degeneration processes associated with aging (Mau *et al*., 2002). Cells must maintain an appropriate balance between levels of free radicals and antioxidants to ensure the structural integrity of vital components. When levels of free radicals exceed antioxidant levels during oxidative stress, sensitive biomolecules such as lipids, proteins, and DNA can be damaged (Lee and Seo, 2006).

In the study (Parwin *et al*., 2019), the researchers indicated that induction of hyperlipidemia led to various tissue lesions in the liver tissue, including apoptosis of hepatocytes and infiltration of lymphocytes with the formation of fibrous connective tissues in the liver and thickening of the walls of the central veins. The researcher attributed the reason to the increase in the formation of free radicals as a result of hyperlipidemia. In a study prepared by (Abdou *et al*., 2018), the researcher indicated that inducing hyperlipidemia leads to hepatocyte degeneration with congestion of the central veins, vacuolar degeneration of hepatocytes, and infiltration of lymphocytes.

Other studies indicated that the fatty diet is the main source of hepatocyte injury, vascular inflammation dilation, inflammation, and fibrosis outcomes after this injury (Al-Awadi *et al*., 2013). Injury to liver tissue due to hyperlipidemia alters its functional capacity for transport and membrane permeability or integrity, leading to leakage of enzymes from hepatocytes that indicates severe damage to hepatocyte membranes (Nishi *et al*., 2002).

Hyperlipidemia leads to oxidative stress due to the generation of free radicals, cellular damage, increased lipid peroxidation processes, effect on cell membranes and weakening of antioxidants where malondialdehyde is formed. Hypercholesterolemia is associated with oxidative stress that results from

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increased production of active oxygen species or impairment of the antioxidant system (Duarte *et al.*, 2009). A study (Xie *et al.*, 2018) found that hyperlipidemia causes liver toxicity by producing free radicals, increasing levels of fat peroxide, increasing MDA generation, and increasing liver aminotransferase enzymes AST, ALT and alkaline phosphatase (ALP), and an increase in hydrogen peroxide H_2O_2 and a decrease in the enzyme antioxidants such as the enzyme superoxide dismutase SOD and the enzyme catalase CAT, respectively, as well as a decrease in the level of GSH.

Negative Effects of Hyperlipidemia on The Aorta

The results of the study (Temel and Rudel, 2007), which found that hypercholesterolemia activates the development of atherosclerosis of the aorta, which often progresses as a result of the continued deposition of fatty droplets between muscle layer fibers. The study (Takahashi *et al.*, 2002) showed disorders in the aorta of the high-cholesterol diet categories, the elastic lamina layer of the artery was significantly damaged, and macrophages and foam cells were discovered in the walls of the aorta, as the formation of macrophages is important for the accumulation of fat within cells and foam cell development in coronary artery disease. A study (Kafi and Al-Ezzi, 2017) showed that when hyperlipidemia was induced in mice, histological lesions in the aorta included the appearance of vacuoles in the sub-endothelial layer, the appearance of vacuoles and the thickness of the inner lining, as well as the infiltration of inflammatory cells around the aorta.

According to the lipid hypothesis, abnormally high cholesterol levels (hypercholesterolemia), which higher concentrations of LDL-C and lower concentrations of HDL-C are closely associated with cardiovascular disease because they promote the development of swelling and atherosclerosis in the arteries (Ballantyne, 1998). It leads to myocardial infarction (heart attack), stroke and peripheral vascular disease(Husain and Ari,2011).

Conclusion

The results of the current review showed that hyperlipidemia leads to an increase in the level of Total Cholesterol (TC), Low Density Lipoproteins Cholesterol (LDL-C), Very Low Density Lipoproteins (VLDL-C) and a decrease in High Density Lipoprotein Cholesterol (HDL-C) in addition to the high level of Triglycerides (TG) and is a predictor of atherosclerosis.

And that the stored fat tissue secretes Leptin hormone , while the insulin resistance increases when obesity is due to the secretion of Resistin hormone, and that the majority of fats are manufactured inside the body by the enzyme HMG-CoA reductase in the processes of manufacturing cholesterol inside the liver, and hyperlipidemia affects human health by raising the level of free radicals and reducing the level of antioxidants, and it increases the concentration of liver enzymes as a result of histological imbalances caused by hyperlipidemia on the histological parameters of the liver, finally, the high level of (LDL-C) resulting from hyperlipidemia leads to the induction of atherosclerosis of the aorta.

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