



THE IMPACT OF HIGH CHOLESTEROL ON THE LIVER OF BOTH MALE RABBITS AND RATS

Mai Abdullah Al-Mesaibih*,

Sanaa Ahmed Khalifa,

Afaf Hadi Hakamiⁱ

Faculty of Science,

Jeddah University,

Kingdom of Saudi Arabia

Abstract:

The purpose of this study is to compare the effect of high cholesterol on the liver of male rabbits and rats. The experimental research methodology was used to conduct this study. The sample of study includes 12 New Zealand rabbits in adulthood at a weight of 2.5 - 3.5 kg and on 16 white rats at puberty at 130-160 gr after data were obtained from the experiments. Then, the experiment was calculated in the Standard Deviation and mean, using the Independent sample test at a time of confidence. 0.05 significant p & $p > 0.05$ not significant, using Statistical Package for Social Sciences (SPSS) v.21 was used for statistical analysis. Finally, the researcher came out with the following results: the animals were dissected, and the most important statistical results obtained were a significant increase in cholesterol, triglycerides, high-density proteins, low-density proteins, liver enzymes (aminotransferase and aspartate aminotransferase) in rabbits compared to rats. Significant changes were also observed in rabbits' liver compared with rat's liver. These changes were manifested in the presence of fatty droplets in the cytoplasm of liver cells and necrosis, the deformation of the region Babiism and expansion of blood pockets and central veins.

Keywords: cholesterol, liver of male rabbits, liver of male rats

1. Introduction

The rise of cholesterol has become a disease of age due to wrong eating habits. Also, because of the spread of fast-food restaurants. Moreover, food saturated with oils and also lack of movement and exercise due to the busy lifestyle of the people and mismanagement of the time which cause stress and depression. Therefore, people spend most of their time sleeping or using their mobiles for too many hours. Thus, they

ⁱ Correspondence: email afaf-hakami@hotmail.com

don't have time to exercise or even walk for 30 minutes a day. All the above-mentioned reasons are quite enough to cause fatal diseases such as heart attack.

According to WHO (2008) report by 2030, diseases caused by high cholesterol, leading cause of death, will affect nearly 23.6 million people worldwide. Added to that Department of Statistics and Information in the Kingdom of Saudi Arabia (2012), mentioned that heart disease and circulatory system, resulting from high cholesterol and obesity are ranked first in the diseases prevalent in Saudi Arabia, which leads to death. Over the past 30 years, with the social development, changing lifestyle and the economic recovery that Saudi Arabia has been experiencing, it has changed the lifestyle and style of food (Harbi, 2004). Also, Masiqar (2001) said that unhealthy diet makes the person obese and prone to serious illnesses and thus affects his health. Therefore, the researcher intended to find out the relationship between food types and a high level of cholesterol. To help to raise the level of awareness among Saudi people and draw their attention to the danger of their eating habits. Also, the researcher seeks to shed light on the association between the lifestyle and high level of cholesterol.

1.1 Objectives of the Study

This study aims to:

- Compare the impact of high cholesterol on the liver of male rabbits and rats.

1.2 The Research Questions

This study attempts to answer the following research question:

- 1) Are there any statistically significant differences in CHOL between the high cholesterol group of rabbits and the high cholesterol group of rats?
- 2) Are there any statistically significant differences in the levels of high-density lipoproteins (HDL) between the high cholesterol group of rabbits and the high cholesterol group of rats?
- 3) Are there any statistically significant differences in triglyceride levels between the high cholesterol group of rabbits and the high cholesterol group of rats?

2. Literature Review and Previous Studies

Laker (2010) indicates that the type of fatty acids in the diet affects health. People who consume large amounts of polyunsaturated fatty acids (olive oil or fish oil) are less likely to develop heart disease than those who eat large amounts of saturated fat. Saturated fatty acids raise cholesterol levels while unsaturated fatty acids do not affect cholesterol levels. The main effect of polyunsaturated fatty acids on blood lipids is to reduce the density of serum triglyceride but does not affect cholesterol.

Al-Awish et al. (2014) reported that when cholesterol levels rise, it is when the cholesterol level rises, it is deposited in the form of fine fatty granules on the walls of the arteries from the inside. The cholesterol deposits increase year by year as the walls of the arteries lose their rubbery properties. The soft texture of those walls, which are necessary for blood flow, is easily transformed into relative roughness. In this case, the

artery is difficult to widen or narrow in response to the blood rush or decrease. This is called atherosclerosis. The amount of blood in the arteries is reduced as the cholesterol is deposited on the walls and the blood clots in the narrowest places in the artery until a complete blockage of that artery. This atherosclerosis disease may affect all or some arteries. If cholesterol levels rise, it is deposited in the form of fine fatty granules on the inside of the arterial walls happens in coronary heart arteries that feed the heart muscle, it causes a heart attack (stroke) There are many factors leads to can cause this such as smoking, high blood pressure, diabetes and lack of exercise, and other sports.

The rats fed on a high diet showed an increase in body weights and significantly increased liver volume. The liver color was yellow and brown, with a surface (Li et al., 2016, Zhou at el.). The high diet caused hypertrophy of hepatic cells and the pressure of the nucleus on the side and the presence of fatty droplets of different sizes and deformation of the liver ribbons as evidenced by increased levels of TC, TG and LDL-C and showed these results indicate that cholesterol plays a crucial role in converting the simple fatty liver towards non-alcoholic fatty liver inflammation.

Wu at el., (2019) observed that rats fed HFD diets high fat accumulation, hepatitis and fibrosis showed significantly increased adhesion molecules in liver tissue and increased levels of GT, LDL, and HDL. Karkhaneh et al. (2016) observed that rats fed high cholesterol diets showed cytotoxicity, degeneration, vesicular polyphagia, increased TC, TG, and LDL-C levels. HDL-C levels were significantly reduced, smooth muscle and proliferative endothelial layer.

3. Materials and Methods

3.1 Methodology

The researcher followed an experimental approach.

3.2 Population and Sample

In this study, the sample consist (12) of New Zealand rabbits in adulthood at a weight of 2.5 - 3.5 kg and (16) of white rats in adulthood at 130-160 g. These animals were obtained from the King Fahd Center for Scientific Research at puberty. The experiment was conducted at the Animal House at the Faculty of Pharmacy at the King Abdul-Aziz University at a temperature between 20-21 °C with 12 hours of lighting and 12 hours of darkness. The animals were left a week to adjust to the place, and placed each individual animal in a plastic cage until the meal is properly adjusted and sawdust was used in rat cages with the provision of water and meal as well as for rabbits and cages were cleaned periodically, and the animals were fed on a standard meal According to the need of the adult animal by (15 grams) per day. Also, the meals, and drinking were prepared water changed daily.

The sample was divided as follows: each type of animal was divided into two groups:

First: rabbits. The first group consists of 4 rabbits, the control group fed to the standard meal. The second group consists of 8 rabbits, the experimental control group that fed the high-fat diet.

Second: rats. The first group consists of 6 rats, the control group fed to the standard meal. The second group consists of 10 rats, the experimental control group that fed the high-fat diet.

All the study animals were dissected two months after the start of the experiment and the liver was removed and cut into small pieces and submerged in the fixer.

3.3 The Research Instruments

a. Cholesterol

The chemically produced cholesterol powder from Hangzhou Dingyan Chem Co., LTD was obtained from China and was mixed with palm oil and placed on the standard meal to ensure that animals were fed high cholesterol (28.75% palm oil -2.5% Cholesterol, Ichimura, (2016).

b. The Palm Oil

Oline palm oil (Haia) was purchased from the supermarket in Jeddah.

3.4 Preparation of the Dose

The oil was heated at 60/70 °C for about 10 minutes to 15 minutes and then gradually put the cholesterol powder on the oil until it melted and then poured on the feed. A dose of 15 g / 100 g body weight per day was given along the length of the experiment, in addition to 4 g of fat, which is found mainly in the standard meal to ensure that the animals are fed high cholesterol (4031).

3.5 Biochemical Study

Cholesterol was measured according to the Schermer method (1967) using a centrifuge to separate the serum Serum from the blood after rabbits and rats were incubated for 12 hours and then anesthetized with Diethylether diuretic, drawing blood from the eye vein of the rats and from the ear to the rabbits. Kidneys (TC), low-density lipoprotein (HDL), high-density lipoproteins (LDL), triglyceride (TRIG), liver enzymes (AST) and (ALT).

3.6 Histological Study

After the experiment was completed, the animals were killed by beheading, dissected and liver samples were placed in neutral buffered formalin 10% solution for 24 hours and samples were then prepared for optical microscopy. Dehydration and then embedded in the paraffin wax, then pruning the wax mold, fixing it into the micron and cutting it with a thickness of 6, then fastening it to glass slides and dyeing it with hematoxylin and iodine.

3.7 Research Procedures

The following procedures were used in order to reach the results. Sample was divided into control and experimental group each type of animals was divided into two groups: the first group: the control group which fed with the standard meal and the second: experimental group, which fed the high-cholesterol diet. During the experiment, the animals were weighed and the level of cholesterol, triglycerides and liver enzymes in the blood were evaluated every two weeks until the end of the experiment.

At the end of the study data, the statistical analysis of all the different variables was done according to the method of Zoghbi and Tarafha (2012), where the body weight and weight of the liver were measured: blood fat, total cholesterol, total lipids, high density lipoprotein, low density lipoprotein (LDL), trig triglycerides. The results of the experiment were calculated in the standard deviation and mean, using the independent sample test at a time of confidence. 0.05 significant $p < 0.05$ & $p > 0.05$ not significant, SPSS v21 was used for statistical analysis.

4. Results and Discussion

Table 1 and Figure 1 compare the effect of fat on rabbits and rats. There is a statistically significant increase in CHOL between the high cholesterol group of rabbits and the high cholesterol group of rats. In rabbits, it was 15.42 ± 0.05 mg / 100) compared with the group of rats (1.682 ± 0.217 mg / 100 ml). There is also a significant increase in the levels of high-density lipoproteins (HDL) between the high cholesterol group of rabbits and the high cholesterol group of rats. 100 ml) compared to the group of rats (1.27 ± 0.18 mg / 100 (0.26 ± 2.69 mg / 100 ml) compared with the group of rats (0.25 ± 0.06 mg / 100 ml) compared to the total group of rats (0.25 ± 0.06 mg / 100 ml). There was also a statistically significant increase in triglyceride levels between the high cholesterol group of rabbits and the high cholesterol group of rats. It was found in the rabbits group (7.87 ± 3.54 mg / 100 ml) compared to the group of rats (0.87 ± 0.09 mg / 100 ml).

Mahfouz and Kummerow (2000) showed that rabbits fed on a high diet led to elevated total cholesterol (TC), high-density lipoprotein (HDL) and triglycerides (TG) during the two months and quadrupled in four months. In mice, however, cholesterol did not rise significantly during the two months, while it began to rise after that.

4.1 Histological Results

A. Experimental Group

The hepatic structure of the liver in rabbits of the control group in the current study with microscopic examination (and until 2013) agrees that the hepatic tissue in the rabbits is composed of hepatic lobes surrounded by connective tissue. These lobes are clear and porous and it is easy to distinguish the lobster in the rabbit (Fig. 2) what distinguishes it from the rat.

The histological structure of the liver in the control group is consistent with the microscopic examination (Qahl, 2015), where the hepatic lobules are not separated by barriers (Fig 3).

The hepatic tissue in the rabbit (Fig. 4) and the rats (Fig. 5) are composed of hepatic cells that are a stranded matrix of a cell or two cells located between the sinus capillaries and the central vein. Hepatic cells have polygonal forms, and the majority of hepatic cells are monoclonal but bioluminescent cells can be observed commonly and this is consistent with Popescu (2012) and Braet et al. (2017). The cells of Kupffer cells are seen in variable forms, from thin to round to massive. The endothelial cells in the blood sinusoid blood pockets are small, dark-colored nuclei that are effective cells for circulatory waste. This is consistent with Poisson et al. (2017) and (2013) and to.

(Fig. 6) and rats (Fig. 7): the presence of the portal space between hepatic lobules, which consists of a portal vein characterized by a thin wall and a relatively large cavity, the hepatic artery with a thicker and relatively narrower wall, bile duct, which is lined with simple cuboid epithelial cells and has a large round or oval cavity. This is what was seen and agreed with the study (Qahl, 2015).

B. High cholesterol control group

The microscopic examination of the cholesterol-infected rabbit liver and rats in the present study showed deformation and dilatation of some central veins and disruption of the reticular structure of cells as a result of the tissue containing cells necrotic atrophic nuclei, and the emergence of merged cellular in some other areas. A sharp spread of fatty drops of different sizes was also seen in the tissue.

A sharp diffusion of fatty droplets of different sizes in the tissue was also observed. It was also observed from the present study that small fat droplets were spread in all rabbit liver tissue while fat droplets were observed to be large in the form of patches in rat liver tissue (Fig. 9.8).

This is in line with the observations of Jian Wang et al. (2011) and Alam et al. (2011), which indicated that there were fat drops in rat liver cells fed high cholesterol meal, as it caused the accumulation of cholesterol and Triglycerides in the liver, and in the form of fatty droplets of different sizes (Fidele et al., 2015).

In the form of (11,10) in the liver of rabbits and rats expansion and tightness in the blood pockets and infiltration of blood fluids and the accumulation of fat droplets inside them and this is referred to Sadeghipour et al., (2014) which observed in rats fed a high-fat diet in breadth the blood pockets, as a result of the accumulation of fatty droplets inside and congested blood compared with the normal group. There is also an increase in Kupffer cells and endothelial cells with varying size and morphological variation compared with the control group. This is an indication (Leroux et al., 2012), which observed the morphological change of Kupffer cells compared to the control group; cholesterol in Kupffer cells is what causes non-alcoholic hepatitis. The results of Roth (1996) confirmed that morphologic markers were found to increase the activity of Kupffer cells, suggesting that fat helped their activity. It was noted that the increase of Kupffer cells in rabbit liver tissue was more consistent than in the rat liver tissue.

Histological changes occurred in the portal space where rabbit liver was observed (Fig. 12): deformation and rupture of connective tissue, fibrosis and deformity

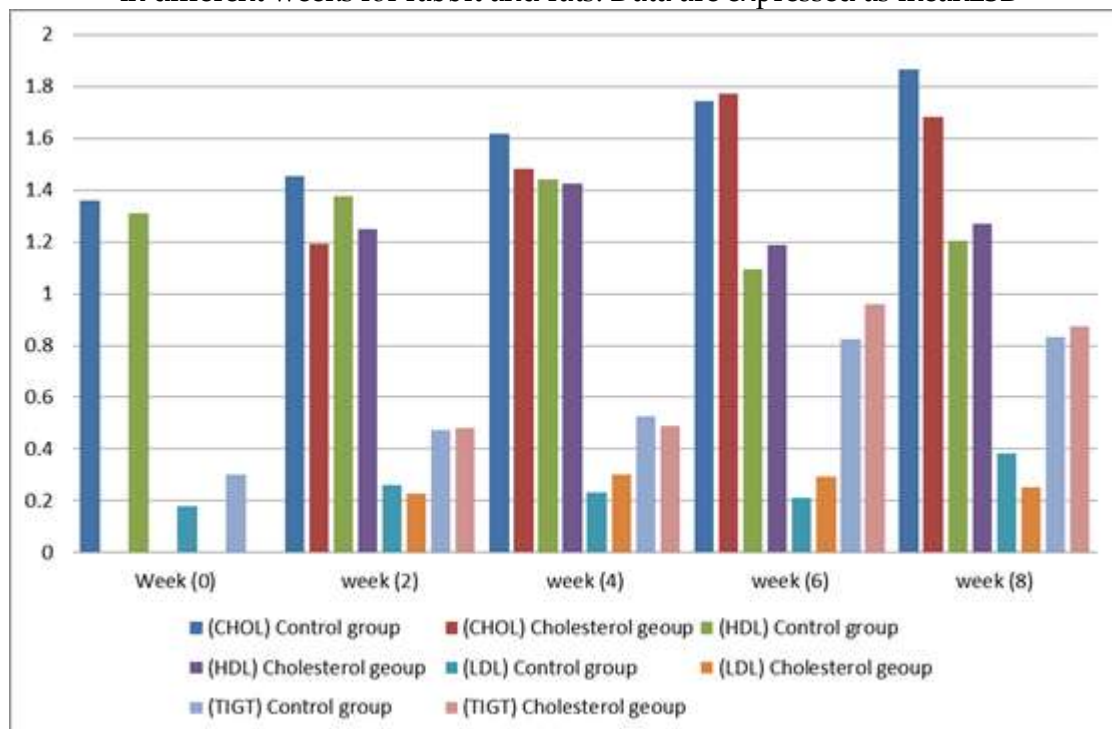
and expansion of the portal artery and proliferation and expansion and deformation of the bile.

In the rat liver (Fig. 13) rupture of connective tissue and fibrosis of the portal space area was also found. While no significant change in the hepatic artery, breeding, stretching and deformation of bile ducts were observed more frequently than rabbit liver. Qahl, 2015) reported changes in the portal space where deformation and congestion in the portal artery and proliferation of bile ducts were observed.

Table 1: Results of serum levels of (CHOL, HDL, LDL, TRIG) (mg/100ml) in different weeks for rabbit and rats. Data are expressed as mean±SD

Rabbits	Rats	Rabbits	Rats	Rabbits	Rats	Rabbits	Rats
1.30±0.00	1.37±0.05	0.42±0.05	1.30±0.06	0.10±0.005	0.18±0.02	0.458±0.043	0.30±0.02
1.30±0.00	1.19±0.200	0.40±0.11	1.25±0.11	0.08±0.05	0.22±0.07	0.530±0.04967	0.48±0.07
P= 0.313		P= 0.000		P= 0.010		P= 0.294	
15.53±0.29	1.48±0.35	3.24±0.86	1.42±0.17	7.60±0.00	0.30±0.17	3.730±1.776	0.48±0.15
P= 0.000		P= 0.001		P= 0.000		P= 0.002	
15.44±0.00	1.77±0.31	3.02±0.46	1.18±0.29	11.53±2.07	0.29±0.10	5.80±3.79	0.96±0.31
P= 0.000		P= 0.000		P= 0.000		P= 0.012	
15.42±0.05	1.68±0.21	3.03±0.47	1.27±0.18	12.26±2.69	0.25±0.06	7.87±3.54	0.87±0.09
P= 0.000		P= 0.000		P= 0.000		P= 0.001	

Chart 1: Serum levels of (CHOL, HDL, LDL, TRIG) (mg/100ml) in different weeks for rabbit and rats. Data are expressed as mean±SD



5. Findings

Grounded on data analysis, in the analysis section, the study came out with the following outcomes:

- 1) There is a statistically significant increase in CHOL between the high cholesterol group of rabbits and the high cholesterol group of rats.
- 2) There is also a significant increase in the levels of high-density lipoproteins (HDL) between the high cholesterol group of rabbits and the high cholesterol group of rats.
- 3) There was also a statistically significant increase in triglyceride levels between the high cholesterol group of rabbits and the high cholesterol group of rats.

6. Conclusions

In conclusion, this research started with the rise of the research problem by reviewing the relevant literature. Research questions that address the research problem were formulated. Finally, the findings of this research were obtained.

In summary, the varieties of body weight, behaviors, levels of total cholesterol in the serum and liver and of lipid in the liver and pathological findings in the autopsy were studied in the rabbits and rats which were fed on the standard diet mixed with cholesterol and fatty oil for a long term of days. The results obtained were summarized as follows:

- 1) There is a statistically significant increase in CHOL between the high cholesterol group of rabbits and the high cholesterol group of rats.
- 2) There is also a significant increase in the levels of high-density lipoproteins (HDL) between the high cholesterol group of rabbits and the high cholesterol group of rats. 100 ml.
- 3) There was also a statistically significant increase in triglyceride levels between the high cholesterol group of rabbits and the high cholesterol group of rats.
- 4) A sharp spread of fatty drops of different sizes was also seen in the tissue.
- 5) A sharp diffusion of fatty droplets of different sizes in the tissue was also observed.
- 6) It was also observed from the present study that small fat droplets were spread in all rabbit liver tissue while fat droplets were observed to be large in the form of patches in rat liver tissue.

6.1 Recommendations

- 1) There should be a daily exercise to avoid the danger of a high level of cholesterol.
- 2) People have to avoid eating any type of food that contains a high level of cholesterol.
- 3) Workshop related to the danger of cholesterol should be held regularly in the Saudi community to spread the level of awareness regarding the issue.
- 4) More studies should be conducted in the community to enlightening them about the more fatal disease such as cancer.

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Appendix

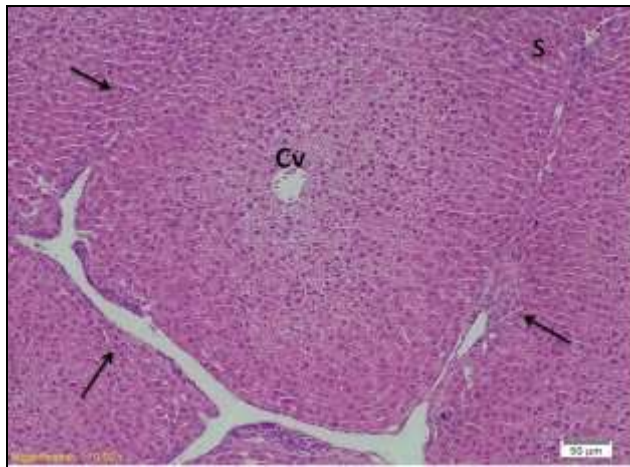


Figure 2: Microscopic photographs of a segment in the rabbit liver of the negative control group showing the lobule (arrow) mediating the central vein (CV) and bloody sinuses (S)

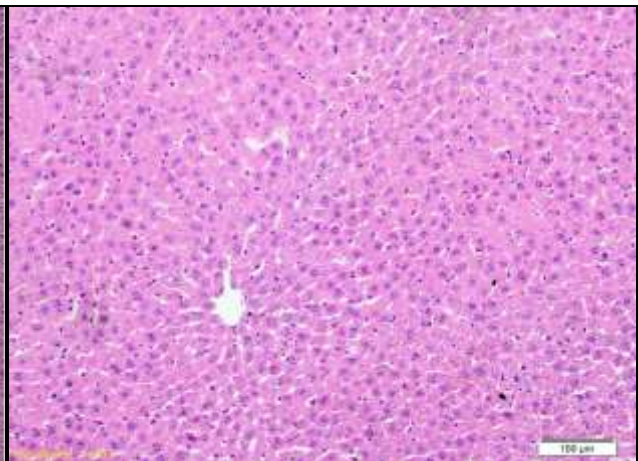


Figure 3: Microscopic photographs of a segment in the rat liver of the negative control group show the lobule shape in the rat not clear

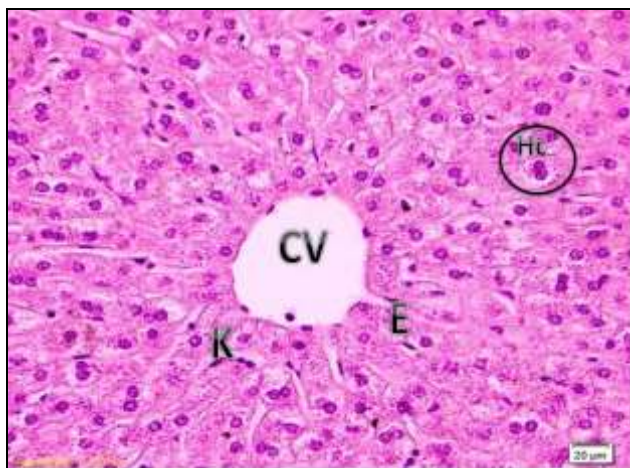


Figure 4: Microscopic photographs of a segment in the rabbit liver of the negative control group showing the central vein (CV) of lined squamous, hepatocellular (HC), kupffer cells (K) and cells and intracellular epithelial cells (E)

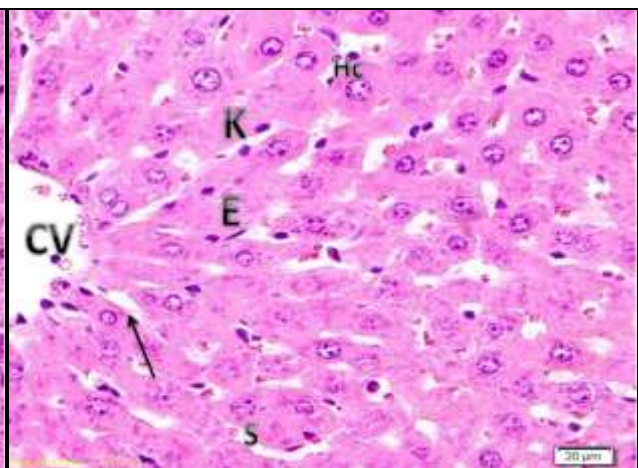


Figure 5: Microscopic photographs of a segment in the rat liver of the negative control group showing (CV) of lined squamous, bloody sinuses (S) and the exit of the ribbons from it clearly (arrow) and the emergence of kupffer cells (K), internal epithelial cells (E) and hepatic cells (HC)

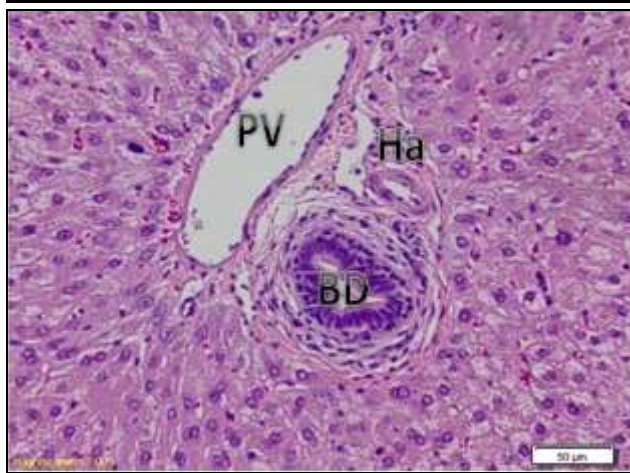


Figure 6: Microscopic photograph of a segment in the rabbit liver of the negative control group showing the portal space (PS) and showing the portal vein (PV), hepatic artery (HA) and bile duct (BD)

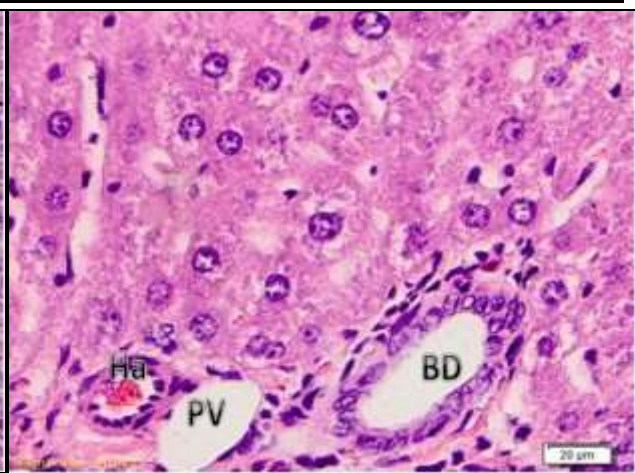


Figure 7: Microscopic photograph of a segment in the rat liver of the negative control group showing the portal space (PS) and showing the portal vein (PV), hepatic artery (HA) and bile duct (BD)

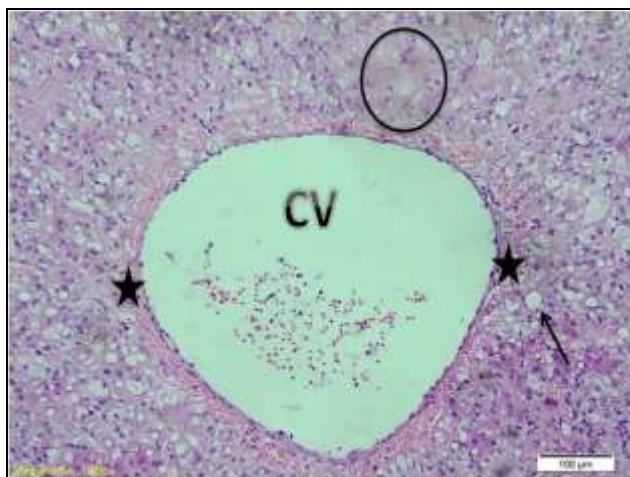


Figure 8: Microscopic photograph of a segment in the rabbit liver of the high cholesterol group shows the appearance of a large dilatation of the central vein (Cv), fibrosis around the central vein (star), diffusion of lipid droplets (arrow) and necrosis of cells (circle)

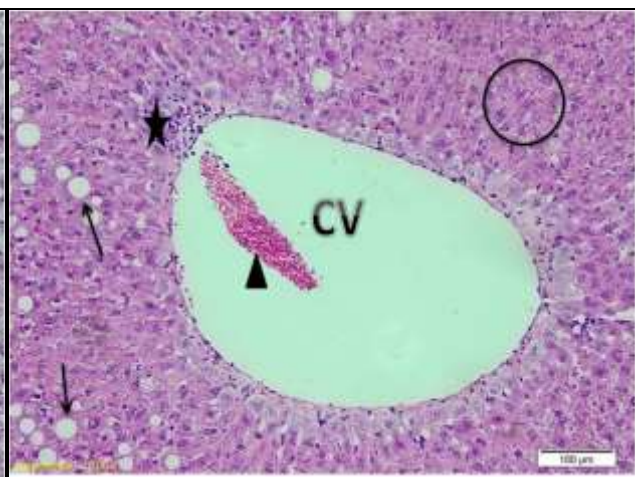


Figure 9: Microscopic photograph of a sector in the liver of high cholesterol group rats shows the appearance of a large expansion of the central vein (Cv) and blood infiltration (arrowhead) with the presence of inflammatory cells (star) and the presence of fat droplets (arrow) and necrotic cells (circle)

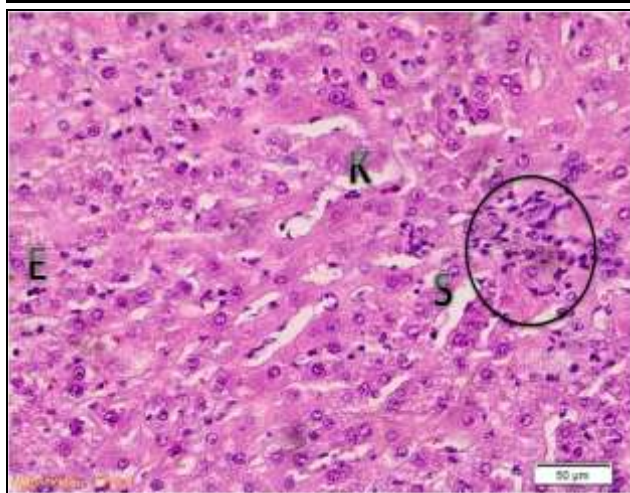


Figure 10: Microscopic photograph of a segment in the liver of high cholesterol group rabbits. An expansion of the bloody sinuses (S) shows an increase, hypertrophy, and change of the morphological shape of Kupffer cells (K), endothelial cells (E) and necrosis cells (circle)

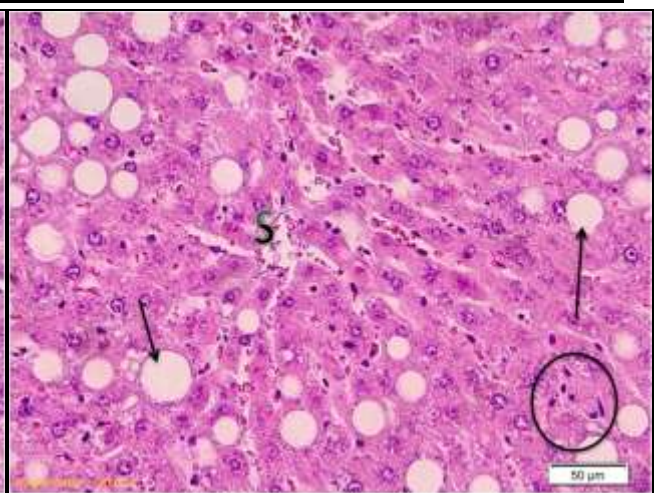


Figure 11: Microscopic photograph of a segment in the liver of high cholesterol group rats shows the presence of a large dilatation of the central vein (Cv) and blood infiltration (arrowhead) with the presence of inflammatory cells (star) and the presence of fat droplets (arrow) and necrotic cells (circle)



Figure 12: Microscopic photograph of a segment in the rabbit liver of the high cholesterol group shows rupture and deformation of the portal space (arrow) and deformation and reproduction of the bile duct (circle)

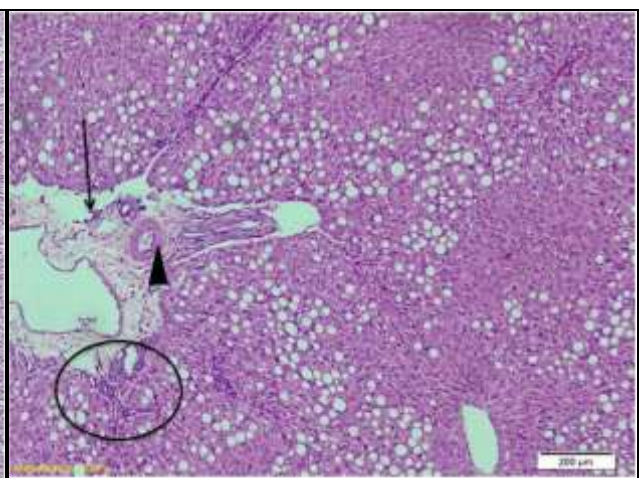


Figure 13: Microscopic photograph of a segment in the rabbit liver of the high cholesterol group shows deformation of the portal space (arrow) and proliferation of bile ducts (circle) and also shows the portal vein (arrowhead)

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