How to Cite:
Al.Shammary, S. M., Hassan, S. S., & Almulla, A. A. (2022). The effect of rusavastatin on glycemic index in hypercholesterolemic adult male rats. *International Journal of Health Sciences*, *6*(S5), 6141–6148. https://doi.org/10.53730/ijhs.v6nS5.10040

The effect of rusavastatin on glycemic index in hypercholesterolemic adult male rats

Sarah M. Al.Shammary
Department of Dentistry, Al Hadi University College, Baghdad, Iraq
Email: sara.mohammed9333489@yahoo.com

Sura S. Hassan
Department of Dentistry, Al Hadi University College, Baghdad, Iraq
Email: biologistsura@yahoo.com

Aussama A. Almulla
Department of Dentistry, Al Hadi University College, Baghdad, Iraq
Email: ausamaalmulla@yahoo.com

***Abstract*---**The present experiment was investigated to study the effect of Rosuvastatin on glycemic index in rats that exposed to hypercholesterolemia. Sixteen matured male rats it was used in that study, were arbitrary chose and identically grouped up in to two coteries as follows C, T. They were dosed by oral intubation (daily) for 42 days as follows; C: control group, were supplied distillated water by dosing needle, T: animals of this group were given Rosuvastatin statin 0.3mg/kg/day/kg/day + 10 g\day cholesterol within diet orally. The daily supplementation of statin enhance i a significant increase in glucose concentration and insulin resistance, also there was significant decrease in insulin hormone & in IGF-1 in (T) group as compared to control group respectively. Moreover, the histopathological examination showed that clear space of fatty degeneration in cardiac muscle fiber, also cross section of liver showed vacuolar degeneration in the hepatocytes with inflammatory cells infiltration around blood vessels in addition to few fatty vacuoles. In conclusion, the results from this investigation approve that rosuvastatin supplementation to rats has an bad effect on heart muscle and hepatic portal system in hypercholesterolemic infected rats.

***Keywords*---**Rosuvastatin, Hypercholesterolemia, Insulin resistance, IGF-1.

1. Introduction

Cardiovascular disease (CVD), considered as a main cause of death in many countries, is a long-lasting disease that lasts without symptoms for decades. Its occurrence rate is expanding in the world. Although the advancing of CVD caused by many factors, hypercholesterolemia is thought to act a basic role in the pathogenesis and amelioration of it [1]. The present-day lifestyle that characterized with high-cholesterol diet (HCD) and less physical activity contribute to hypercholesterolemia which lead to progress the currency of CVD [2] .In addition to that, high blood cholesterol level can lead to the occurrence of nonalcoholic fatty liver disease (NAFLD), which is a metabolic dysfunction which have a clinical importance and considered as the most familiar cause of liver function abnormalities. NAFLD is illustrated by a sever liver damage, like simple steatosis, fibrosis and cryptogenic cirrhosis [3].Hence, to control the development of CVD and NAFLD we must controlling plasma cholesterol or preventing hypercholesterolemia. Inspite of that there is a medical cure available for treating hypercholesterolemia, the consuming of dietary supplements/functional foods in lowering/controlling serum cholesterol levels and risk of CVD and NAFLD has accomplished universal acceptance over the years by the public [4] .Statins are widely described in the treatment of hypercholesterolemia, can accomplish 20%–50% to reduce cholesterol levels and have been linked to the reduced the occurrence of coronary morbidity and mortality in high-risk adults [5].

2. Materials and methods

2.1 The animals of experiment and its cure

Local sixteen male Albino Wistar rats in good health (3 -4) months in age, and weighted from 190 –200 gram (g) were captured from the drug control center /ministry of health and reared in the animals house of the Veterinary Medicine College / Baghdad university within a period extended from February to April,2022**.** They were reared in idial condition of 20-25 °C in a well-ventilated room and photoperiod of 12 hours per day.The animals were housed at least two weeks for acclimatization before beginning the experiment**.** During this period these animals was given Anticoccidiosis (Amprolium) via drinking water (1g/litter) for three days.

2.2 Preparation of Rosuvastatin

One tablet contain 20 mg of rosuvastatin was dissolved in 20 ml distilled water, then we took 2.8 ml from it ,to dilute it in 10 ml distilled water for each 100 g\B.W. Were given orally to male rats at a dose of (1.4mg\kg\day) by using gastric intubation [6].

2.3 Preparation of cholesterol

Diet rich with cholesterol were given to these animals with concentration of cholesterol 10 g per kg of diet [7].

2.4 Blood samples collection

Fasting blood was obtained via cardiac puncture from each rat at the end of the (42 day) of the experiment. Blood serum samples was obtained after centrifugation at a speed of 3000 revolution/minute (rpm) for 20 minutes. These samples were stored in a freezer at -18 °C until use [8].

2.5 Experimental design for the experiment

After accomodation for two weeks we divided the animals identically into two groups, (C) control group which got distillated water each day, (T) group which receive (1.4mg\kg\day) of statin plus high cholesterol (10gm\day) orally.

2.7 Statistical analysis

In this study one-way ANOVA used for performing statistical analysis. Least significant differences (LSD) to assess significant differences among means of the groups by using the SAS [9].

3. Results and Discussion

3.1 Effect of rosuvastatin on serum glucose concentration (mg/dl)

Table (1) marked that mean values of serum glucose concentration after (42) days of experiment low significantly increase after oral intubation of statin (T) comparing to (C) control group, at the end of the experiment, the mean values of this parameter were (94.62±0.98) for control group and (105.87±0.98) for (T) group.

3.2 Effect of rosuvastatin on serum insulin concentration (µIU/ml)

Table (2) indicated that mean values of serum insulin concentration after (42) days of experiment low significantly decrease after oral intubation of statin (T) comparing to (C) control group, at the end of the experiment, the mean values of this parameter were (18.86±0.28) for control group and (16.67±0.43) for (T) group.

3.3 Effect of rosuvastatin on insulin resistance

Table (3) indicated that mean values of insulin resistance after (42) days of experiment no significant increase after oral intubation of statin (T) comparing to (C) control group, at the end of the experiment, the mean values of this parameter were (4.40±0.05) for control group and (5.00±0.06) for (T) group.

3.4 Effect of rosuvastatin on serum insulin like growth factor 1 concentration (nmol/L)

The results of serum insulin like growth factor 1 in table (4) showed that the mean values after (42) days of experiment low significant decrease after oral intubation of statin (T) comparing to (C) control group, at the end of the

experiment, the mean values of this parameter were (1764.95±50.08) for control group and (1350.88±2.05) for (T) group.

3.5 The effect of rosuvastatin on the histopathology of liver and heart

Our current study has been valided in hypercholesterolemic adult male rats, exhibiting clear contractile dysfunction characterized by decreased maximum rate of shortening, lowest rate of relaxation, and increased left ventricular end-diastolic pressure [15] .Dyslipidemai, insulin resistance, low adiponectin, and postprandial dyslipidaemai and hyperglycaemia are main factors lead to NAFLD and further aggravate the course of NAFLD as well as accelerate the progress of atherosclerosis and development of CVD [10].

Histopathological findings of liver of rats received statin (1.4mg/kg/day) plus(10 g\day) cholesterol within diet showed few fatty vacuoles, and vacuolar degeneration in the hepatocytes with inflammatory cells infiltration around blood vessels.Also histopathology of heart to the same group showed clear space of fatty degeneration in cardiac muscle fiber.

Table 1 Effect of rosuvastatin on serum glucose concentration

Groups / Parameter	C Intact Rats Received distillated water	T Rats received rosuvastatin+pure cholesterol
Glucose (mg/dl)	94.62±0.98	105.87±0.98

Table 2 Effect of rosuvastatin on serum insulin concentration

Groups / Parameter	C Intact Rats Received distillated water	T Rats received rosuvastatin+pure cholesterol
Insulin (g)	18.86±0.28	16.67±0.43

Table 3 Effect of rosuvastatin on insulin resistance

Groups / Parameter	C Intact Rats Received distillated water	T Rats received rosuvastatin+pure cholesterol
Insulin Resistance (g)	4.40±0.05	5.00±0.06

Table 4 Effect of rosuvastatin on insulin like IGF-1 concentration in serum

Group / Parameter	C Intact Rats Received distillated water	T Rats received rosuvastatin+pure cholesterol
IGF-1 (g)	1764.95±50.08	1350.88±2.05

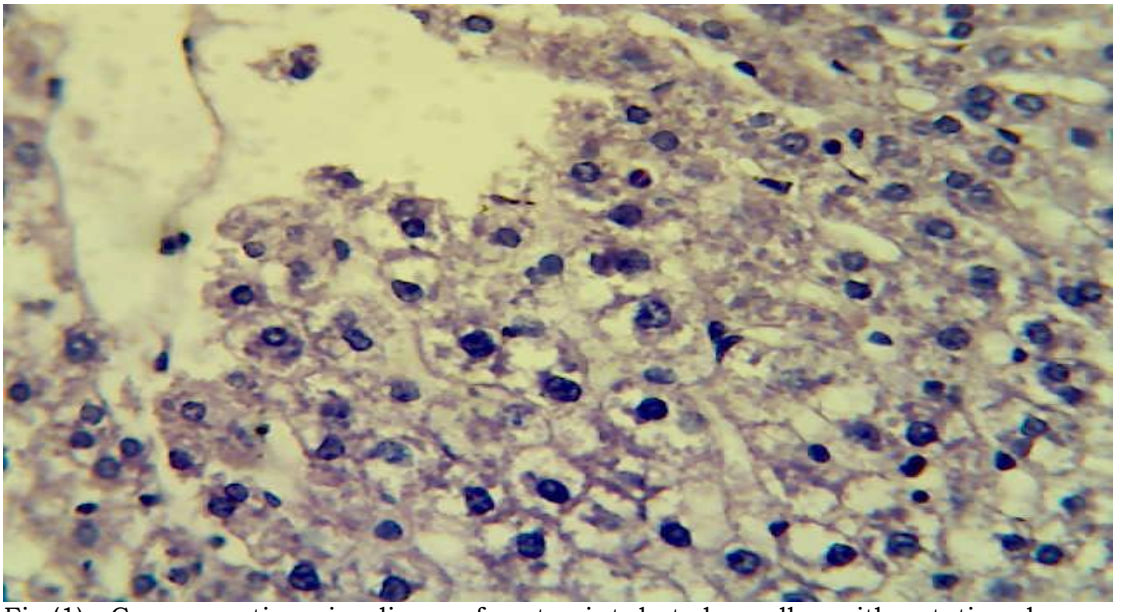

Fig.(1) Cross section in liver of rats intubated orally with statin drug (1.4mg/kg/day) + Pure cholesterol (10g/kg/day) shows few fatty vacuoles (H and E stain 400X).

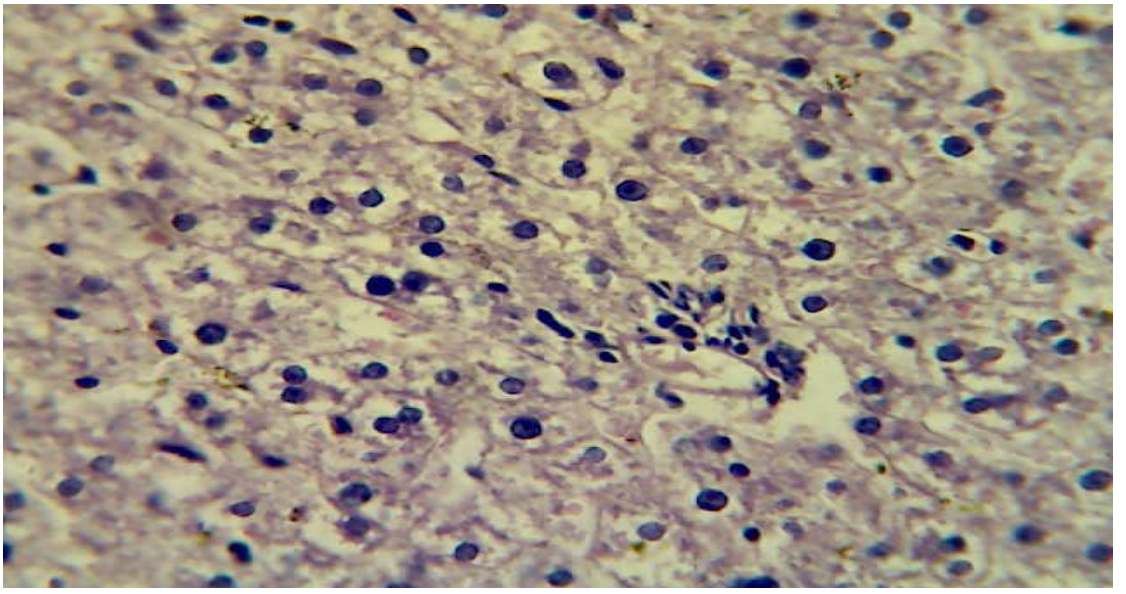

Fig.(2) Cross section in liver of rats intubated with statin drug (1.4mg/kg/day) + Pure cholesterol (10g/kg/day) shows vacuolar degeneration in the hepatocytes with inflammatory cells infiltration around blood vessels in addition to few fatty vacuoles **(**H and E stain 400X).

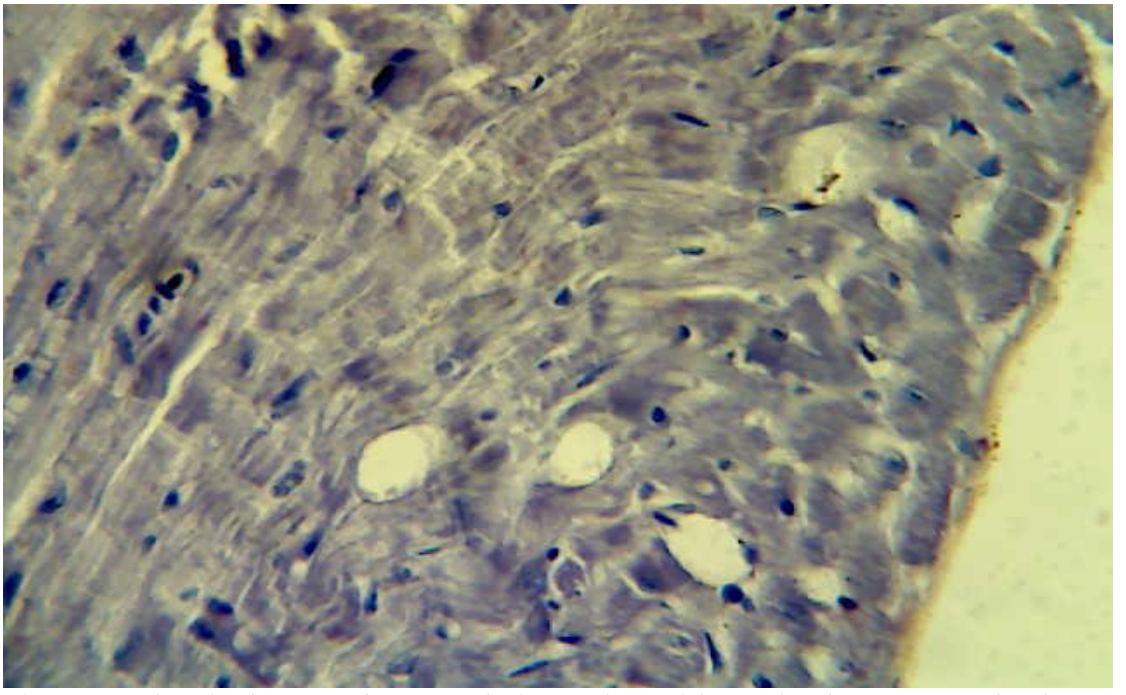

Fig.(3) Section in heart of rats adminstration with statin drug 1.4mg/kg/day shows clear space of fatty degeneration in cardiac muscle fiber **(**H and E stain 400X).

4. Conclusion

In vitro studies have identified possible mechanisms by which rusovastatin affects glucose metabolism. These include the inhibition of insulin secretion, possibly by decreasing GLUT2 activity, reducing ATP production, inhibiting L-type Ca2+ channels and decreasing cytosolic Ca2+ concentrations. Some studies have reported that simvastatin may impair glucose metabolism whereas other studies reported no effect or improvement of glucose metabolism. Even though statins are beneficial in reducing the risk of cardiovascular events, its glycemic effect on patients should be monitored by periodically evaluating blood glucose levels regardless of whether the patients have diabetes or otherwise.

Further studies are required to investigate the possible synergistic effects of statins with concurrent medication on glycemia, especially in patients with multiple comorbidities. Although the benefits of statins have been shown to outweigh its risks, it is important that glycemic control in patients is monitored for potential drug interactions between statins with the concurrent medications used. Besides that, further studies are recommended to determine whether or not the dose and duration of statin use could affect the glycemic control.

5. Acknowledgments

Authors would like to express our sincere thanks first of all with deepest from the core of my heart and praise it to almighty Allah, also deep appreciations and sincere thanks are paid to the Dean of Al Hadi University college *Prof Dr.Mahmoud Al Obaidy ,* and my best teacher ever *Prof Dr.Khalissa Khudhair*

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