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Effects of Two Types of Statins in Lipid Profile of Ovarictomized Female Rats

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A B S T R A C T

Statins are the most important drugs that used widely in reducing cholesterol and lipids related with cholesterol and vascular heart diseases prevention, through HMG-Coenzyme reductase inhibition. Statins classified into two types: hydrophilic and lipophilic. The current study was carried out to clarify whether simvastatin or rosuvastatin the better in serum lipid profile of ovariectomized female rats which used as a model for postmenopausal women who has hyperlipidemia. Twenty four adult female rats aged (2.5-3) month and weight (220-250) gm were grouped into four groups (6/group): control group (sham): without ovariectomy, ovariectomized (ovx) group, ovariectomized (ovx) rats that administrated by 20 mg/kg/day (orally) with rousvastatin and ovariectomized (ovx) rats that administrated by 20 mg/kg/day(orally) with simvastatin. After experiment period 60 day. Samples of blood were drawn and lipid profile were estimated. The results were showed that ovariectomy operation caused a significant elevation in total cholesterol, triglyceride, low density lipoprotein-cholesterol (LDL-c), very low density lipoprotein-cholesterol (VLDL-c), non-HDL-c, and decrease in high density lipoprotein-cholesterol (HDL-c), but the treatment of ovariectomized rats with rosuvastatin caused a greater reduction in the level of serum total cholesterol and LDL-c than simvastatin, however, simvastatin showed a greater drooping in serum triglycerides, VLDL-c and also non-HDL-c. We concluded that there are differences in activity between simvastatin and rosuvastatin in lipid profile and the rosuvastatin has the effectiveness in total cholesterol and LDL-c reduction.

Introduction

Hyperlipidemia is a condition characterized by high levels of lipids in the blood[1]. It is a metabolic disorder that is considered a major risk factor for the progression of coronary heart disease [2]. Hypercholesterolemia recently increased because the development in life style, also to the increase in fatty diet consumption[3]. Statins are a type of drugs that is greatly used for decreasing low density lipoprotein cholesterol (LDL-c) also to protect from cardiovascular disease [4]. Statins reduce cholesterol biosynthesis through the inhibition of hydroxymethyl glutaryl-co-enzyme A reductase (HMG-CoA Reductase) [5]; therefore, statins medication is used to reduce risk of the complications of atherosclerosis[6]. The efficacy of statins is varied depend on their pharmacokinetics and structures, and they are classified into two types, hydrophilic and lipophilic statins. The absorption of hydrophilic statins by tissues is slight, therefore they have minimum side effect. Whilst the lipophilic statins penetrate muscles and are absorbed easily [7]. The rosuvastatin(Ros) is a synthetic agent and a hydrophilic statin, that it has hepatic selectivity property[8]. The rosuvastatin has a lower metabolism by the system cytochrome p 450, therefore the interaction of it with another medicines is low[9]. Simvastatin(Sim) is a lipophilic type of statins that used for the hypercholesterolemia and dyslipidemia treatment. Furthermore, simvastatin can affect the genes involved in cholesterol and lipids by regulating the mRNA of these genes [10]. Simvastatin can cross the blood-brain barrier [11].

Menopause in women also ovariectomy in animals are related to the elevation the levels of low-density lipoprotein cholesterol LDL-c and total cholesterol in serum [12]. Ovariectomy is a standard experimental model of rodent to investigate postmenopausal women [13]. The menopause is characterized by the progressive decline of endogenous estrogen levels and the ovariectomy operation act as a model of hyperlipidemia that inducing by estrogen deficiency [14].

The purpose of the current study was the comparing the effects of the two types of statins drugs, lipophilic one (simvastatin) and hydrophilic one (rosuvastatin) in the lipid profile of hyperlipidemic rats caused by ovariectomy.

Materials and Methods

1. Laboratory animals and Experimental Design: Twenty-four females albino rats (2.5-3) months, weighting (220-250) gm were maintained under conditions of temperature between (22-25) C^{o}, 12h light-12h dark in the animals house in college of veterinary medicine of Mosul university. Standard diet, also water were given to all the rats . After that the animals were grouped randomly into four groups, 6 rats/group:

   Group 1: Sham operated (control) group, were received distilled water.
   Group 2: Ovariectomized (OVX) rats, were received distilled water.
   Group 3: Ovariectomized (OVX) rats that were received 20 mg/kg/day Simvastatin(Sim) orally.
   Group 4: Ovariectomized (OVX) rats that were received 20 mg/kg Rousvastatin(Ros) orally.

2. Ovariectomy operation: A combination of 2% xylazine (7.5 mg/kg) and 10% ketamine hydrochloride (75 mg/kg) was given for anesthesia rats intraperitoneally [15], so the inability of the wink reflex, in addition to the foot, was used to estimate the succession of the anesthesia process. Sterilization was used before the incision of the skin and removing of the hair in the area of abdomen by using a sharp blade with soap, and povidine iodine was used for sterilization of the area by creating a longitudinal incision, the abdominal place was opened, and then the ovaries were deracinated. After that, the abdominal layers and skin were sutured (vicryl 2/0 and silk 2/0, respectively). In the group of sham, the operation performed without removing ovaries, since because rats have stress responding from operation. All rats were placed in their cages after recovering from the anesthesia [16].

3. Collection of blood samples: After the experimental period 60 day blood samples were withdrawn from the optical vein, then leaving it to clot, after that centrifuged 15 min, serum samples were separated, then stored in(-18 C^{o}) in order to estimate the biochemical parameters [17].

4. Biochemical tests examination: The lipid profile in serum was analyzed by spectrophotometrically. Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) estimated using Biolabo kits [18], and using the Friedewald equation to estimate low-density

lipoprotein cholesterol (LDL-C) as this equation : LDL-C = (total cholesterol)- ((HDL-C) +(VLDL-C)). And very low-density lipoprotein cholesterol was calculated using this equation TG/5. Finally, non-HDL cholesterol calculated via subtracts HDL-C from total cholesterol [19].

Statistical Analysis

One way analysis of variance ANOVA test was applied for analyzing the data, which were expressed as means ± standard deviation SD, using SPSS selector test that was used for detecting the statistical significance between all the groups at probability $p \leq 0.05$ [20].

Results

The results of Table 1 showed, that total cholesterol, triglyceride and VLDL-C were a significant $p \leq 0.05$ elevated in the ovariectomized rats in comparison to the sham group. However, treatment ovariectomized rats by simvastatin led to decreasing in total cholesterol, triglyceride also a significant $p \leq 0.05$ decreasing in very low density lipoprotein cholesterol. Also treatment the OVX rats with rosuvastatin caused a significant $p \leq 0.05$ reduction in the total cholesterol, triglyceride also VLDL-C compared to sham groups, However rosuvastatin treated group revealed a greatest reduction in cholesterol level compared the simvastatin group, but simvastatin shows a greatest reduction in serum triglyceride group.

Table 1. Effects two types of statin in total cholesterol, Triglycerides and VLDL-c in serum rat

Treatments	TC mg/dl	TG mg/dl	VLDL-c mg/dl
Control	126.60±11.14c	97.60±29.67b	19.51±5.93b
OVX	161.94±4.74a	116.21±28.52a	21.43±3.69a
OVX+Sim	95.06±6.41b	63.32±8.20d	12.66±1.64d
OVX+Ros	90.49±8.99d	81.97±15.25c	13.82±4.93c

Different letters in the column mean a significantly different between the groups.

Values represent as mean± SD for 6 animals/group.

The ovariectomy operation results in a significant elevation in LDL-c and non-HDL-c also a significant $p \leq 0.05$ reduction in HDL-c in comparison with sham group. as shown in Table 2, However LDL-c and non-HDL-c reduced in rosuvastatin treated group and the results showed a greatest reduction in LDL-c in OVX group that treated with rosuvastatin. In addition HDL-C elevated in both groups, that treated with simvastatin and in the group that treated by rosuvastatin when comparison to OVX group. But the elevation is more in group that treated with rosuvastatin than the group that treated with simvastatin.

Table 2. Effects two types of statin in LDL-c, HDL-c and non-HDL-c in serum rats

Treatments	LDL-c mg/dl	HDL-c mg/dl	non-HDL-c mg/dl
Sham(Control)	65.75 ± 5.68^{d}	66.92 ± 7.31^{a}	59.68 ± 1.57^{b}
OVX	104.59 ± 2.06^{a}	30.92 ± 2.67^{d}	131.02 ± 3.68^{a}
OVX+Sim	74.11 ± 6.41^{b}	54.66 ± 3.16^{b}	40.40 ± 2.79^{d}
OVX+Ros	55.71 ± 3.31^{c}	41.38 ± 1.30^{c}	49.11 ± 2.19^{c}

Different letters in the column mean a significantly different between the groups.

Values represent as mean± SD for 6 animals/group.

Discussion

This study was planned to estimate the differences among simvastatin(lipophilic statin) and rosuvastatin(hydrophilic statin) in lipid profile of ovariectomized rats. The ovariectomy operation has been done in order to induce menopause conditions, menopause stage is a physiological conditions in the women's life, this stage characterized by deficiency of estrogen and losing the ovarian its functions, also eternal cessation of the menstruation[14]. Several studies referred that menopause has a relation to increasing the coronary heart disease risk, due to alteration in lipid profile [21,22]. The overiectomy operation considered a model of estrogen deficiency in which mimics postmenopause women, that has a relation to hyperlipidemia, hyperglycemia and insulin resistance [23]. This model of surgery induced menopause, the estrogen deficiency affect lipid levels[13]. In our study, ovariectomy operation led to a significant elevation in serum total cholesterol, triglycerides and VLDL-c, this findings agree with results of [24], they noticted a significant elevation in triglyceride, LDL-c and total cholesterol in ovaciectomized rats, also our findings agree with [25] they reported, that postmenopausal women exhibited alteration in lipid, also in lipoprotein metabolism, since serum cholesterol, triglyceride and LDL-c elevated after menopause, they attributed these findings to the intestinal absorption of lipids that increased, in addition to the biosynthesis elevation of cholesterol. The elevation of LDL-c in ovariectomized rats in our study, agreed with[26]. The elevation of total cholesterol in ovariectomized rats of our study may be related to the down regulation in the enzymes expression, that involved in synthesis of bile acids and decreasing cholesterol moving from the blood stream [27].The estrogen deprivation in ovariectomized rats lead to these changing in lipid profile [28,29] who showed that estrogen deficiency caused an elevation in total cholesterol, triglyceride and LDL-c and decreased HDL-c. The elevation of VLDL-c in this study agreed with result of[30], they reported a significant elevation in VLDL-c, also in total cholesterol and triglycerides compared with control group. Also our study releaved a significant decrease in HDL-c in ovariectomized group this agreement with findings of [30] they reported that estrogen deficiency led to alter the peroxime proliferator-activated receptor-expression which is important in lipid metabolism[31]. Also, estrogen deficiency causes a disorder in HDL formation result from dysfunction in lipoprotein synthesis. In addition, the lipid metabolism disorder results form, the defect in the lipoprotein lipase that utilize triglycerides[32]. In this study, simvastatin gave a greater elevation in HDL-c when compared with rosvastatin group. Non-HDL-c also significantly increased in ovariectomized group, this may attributed to all disorders that caused by estrogen deprivation. The ovariectomized group treated with simvastatin, also the group that treated with rosvastatin exhibited a significantly reduction in the total cholesterol, Triglycerides, VLDL-c, LDL-c also non-HDL-c with a significant elevation in the HDL-c, However the preference in lowering the total cholesterol and LDL-c was for rosuvastatin, whilst the simvastatin was the best in lowering triglycerides, VLDL-c and non- HDL-c and increasing HDL-c, this findings close to results of [33] since they reported an elevation in HDL-c. The potency of rosuvastatin in decreasing the total cholesterol and LDL-c in this study agree with results of[34]they reported, about 46-55% reduction in the LDL-c comparison to another types of statins, in addition they noted an elevation 7% in HDL-c when used rosuvastatin in 10-40 mg/day doses, and when compared rosuvastatin with atorvastatin, they noted the lowering effects of rosuvastatin that represent 3 fold other than type. In our study the effect of simvastatin and rosuvastatin in lipid profile was evaluated, the effectiveness of rosuvastatin in lowering the total cholesterol and LDL-c may be due to rosuvastatin effects in correcting the expression of gene reduce the markers which involved in metabolism of cholesterol in ovariectomized rats [35]. The elevation in VLDL-c in ovariectomized rats in this study concert with results of [36]. This elevation in VLDL-c in ovariectomized rats may be due to the reduction in gene that considered a key marker for VLDL synthesis [37]. Both types of statins that were used in our study has a different impact on lipid profile. Rosuvastatin is hydrophilic statin and it is less tissue absorption, so it has less negative effects, but simvastatin is lipophilic statin and it has low bioavailability and this type has adverse effect and causes toxicity for muscle [38]. Hyperlipidemia have been reported as a common metabolic disorder greatly caused by high-fat diet consumption [39,40]. The efficacy of statins is varied depending on their pharmacokinetics and structure, since the statins grouped into two types, hydrophilic one like rosuvastatin which is less absorbed through the tissues, so it has low side effects, while the other type of statins is lipophilic like simvastatin which is has extensive passing through liver and low bioavailability [41]. The decrease in LDL-c by using rosuvastatin in this study agree with findings of [42,43]they reported that, rosuvastatin has ability to decrease the LDL-c in hypercholesterolemic menopausal women. The effect of rosuvastatin in lowering the total cholesterol and LDL-c may be due to rosuvastatin effects in the regulatory key molecules like Low density lipoprotein receptor(LDLR), Proprotein convertase subtilisin kexin 9 (PCSK9) , Sterol regulatory element binding protein -2 (SREBP-2), Low density lipoprotein receptor –related protein -1 (LRP-1) that have a role in metabolism of cholesterol and they accountable for clearance the lipoprotein remnants in circulation [44] also agree with results of [45]. We concluded from this study, that estrogen deficiency is associated with lipid profile alterations and rosuvastatin has the preference in lowering cholesterol and LDL-c, but simvastatin is best in raising HDL-c.

Conclusion

The current study revealed the effectiveness of rosuvastatin comparable to simvastatin in lowering total cholesterol and LDL-c and preference of simvastatin in elevation HDL-c.

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Conflicts of Interest: None.

Ethical approve: The approval of ethics for the current study was obtained from the laboratory animals housed in the College of Veterinary Medicine of Mosul University with a number of approvals UM.VET.2022.038.

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