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The effect of statins on PCSK9 and LDLR gene expression in experimentally dyslipidemic rats

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Dyslipidemia, is a well-established major risk factor for atherosclerotic cardiovascular disease (ASCVD). Low-density lipoprotein cholesterol (LDL-C) serves as the primary transporter of cholesterol within the bloodstream. The LDLR is influenced by multiple factors, including statins and the proprotein convertase subtilisin/kexin type 9 (PCSK9). Therefore, this study aims to evaluate the effect of 2 types of statins on PCSK9 and LDLR gene expression in dyslipidemic rats. The objective of this work was to induce dyslipidemia in adult male rats by the administration of a high-fat diet. The 36 adult rats used were categorized into: the control group (C), which was administered a standard diet for 8 weeks, while dyslipidemia was induced in the rest of the animal groups (A, D) by a high-fat diet for 8 weeks (dyslipidemia groups). The dyslipidemic groups were treated with two types of statins (pitavastatin and atorvastatin) for a duration of 4 weeks. The gene expression of PCSK9 and LDLR was subsequently evaluated. Pitavastatin led to an approximately 15-fold increase, while atorvastatin resulted in approximately an 18-fold increase in PCSK9 gene expression relative to pretreatment values. Regarding LDLR, pitavastatin resulted in approximately a 7-fold increase, while atorvastatin resulted in approximately a 2-fold increase in LDLR gene expression in comparison to pretreatment values. It can be concluded that treatment with both statins over 4 weeks caused an increase in the expression of LDLR and PCSK9 genes, where atorvastatin was slightly more effective in increasing PCSK9 gene expression and pitavastatin was more effective in increasing LDLR gene expression.

Keywords: Dyslipidemia; LDLR; PCSK9; rats; statins.

Introduction

Dyslipidemia is a condition characterized by an imbalance of lipids, including cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein (HDL). In clinical practice, dyslipidemia is classified as either primary or secondary based on its pathogenesis. Subdivision may also be based on biochemical alterations, such as isolated elevations in total cholesterol (TC) or triglycerides (TG), low isolated levels of high-density lipoprotein (HDL) cholesterol, and concurrently elevated TC and TG accompanied by low HDL cholesterol levels (mixed or combination) (Mosca et al., 2022).

The most commonly associated clinical outcome of dyslipidemia is increased atherosclerotic cardiovascular disease (ASCVD) risk (Berberich & Hegele, 2022). It may stem from multiple sources, including nutrition, tobacco exposure, genetics, age, sex, alcohol consumption, hypertension, body weight, metabolic syndrome, and abdominal obesity (Al-Hayali et al., 2024; Cheraghian et al., 2025). High cholesterol causes several physiological disorders, including obesity, heart disease, and Alzheimer's disease (Raheem et al., 2023). A diet rich in processed foods, combined with excessive alcohol consumption and insufficient physical activity, exacerbates lipid imbalances and increases the likelihood of conditions such as atherosclerosis and metabolic syndrome (Jiang et al., 2021). High-fat diets induce the development of metabolic syndrome, with a high incidence of oxidative stress, atherogenic dyslipidemia, a pro-inflammatory and pro-thrombotic state, high blood pressure, central obesity, and cardiovascular disease (Andersen & Fernandez, 2024). While dietary animal fats provide additional cholesterol, their intake has a significant impact on total cholesterol levels. As a result, fatty deposits or plaques build up in the arteries, narrowing or clogging the lumen and limiting blood flow (Fancher et al., 2018). However, LDL particles contribute to the formation and progression of atherosclerosis. Atherosclerosis is presently recognized as a systemic, chronic inflammatory condition of the arterial wall. The quality of lipoprotein particles is crucial. Modification in the structure of lipoproteins affect their functional properties and, consequently, their involvement in atherogenesis (Vekic et al., 2022). LDL particles are produced via the delipidation process of very low-density lipoproteins (VLDL) and serve as the primary transporters of cholesterol in plasma. LDL particles contain one apoB molecule, which is recognized by specific LDL receptors. Circulating LDL particles exhibit significant heterogeneity in terms of their density, size, and lipid composition, leading to the formation of various unique subfractions (Rizzo & Berneis, 2006). LDL receptors (LDLR) enable the uptake of LDL-C from the bloodstream into cells, which is essential since LDL functions as the principal carrier of cholesterol (Bao et al., 2024). LDLR facilitates LDL absorption and is crucial for the elimination of plasma LDL-C (Goldstein & Brown, 2015). LDLR binds to LDL and is internalized through clathrin-coated pits, subsequently transported to endosomes. Here, LDL is released from the receptor and directed to the lysosome for degradation, while LDLR is recycled back to the cell surface (Rudenko et al., 2002). Familial hypercholesterolemia which is caused by mutations in LDLR, increases the risk of atherosclerosis and coronary heart disease. Sterol regulatory element-binding protein 2 (SREBP-2) controls the transcription of LDLR (Alabi et al., 2021). On the other hand, proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein predominantly secreted by the small intestine, liver, and kidney, is involved in the catabolism of LDL-C through its interaction with hepatic LDLRs, facilitating the transport of LDL-C from plasma into hepatocytes (Guo et al., 2021). The interaction between PCSK9 and LDLR causes the degradation of LDL receptors in the lysosome, resulting in reduced LDLR expression on the hepatocyte membrane and consequently elevated plasma LDL-C levels (Horton et al., 2007).

However, statin therapy is frequently employed to manage hypercholesterolemia through the inhibition of hepatic cholesterol synthesis (inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR)), the upregulation of LDLRs, and the promotion of LDL

clearance from plasma, ultimately leading to a reduction in cardiovascular disease risk. Statins, such as atorvastatin, lovastatin, pitavastatin, and rosuvastatin, are primarily intended to lower plasma cholesterol levels and prevent cholesterol synthesis (Yaseen et al., 2025). Statins presumably modulate various critical vascular biological processes owing to their pleiotropic beneficial actions, which encompass cholesterol lowering, anti-inflammatory, antioxidant, antiproliferative, and additional mechanisms (Bahrami et al., 2020). Many individuals on statins do not meet the recommended LDL-C targets (Laufs et al., 2019), and a significant proportion of patients may exhibit intolerance to these medications (Bytyçi et al., 2022). Numerous novel LDL-lowering agents have been developed as a consequence of this. The efficacy of statins in lowering plasma LDL-C levels is limited by the paradoxical elevation in circulating plasma PCSK9 linked to statin treatment (Mahjoubin-Tehran et al., 2024). Therefore, this study aims to evaluate the effect of two types of statins as lipid-lowering agents on PCSK9 and LDLR gene expression in rats with dyslipidemia.

Materials and methods

This study received approval from the Institutional Animal Care and Use Committee of the College of Veterinary Medicine at the University of Mosul, Iraq, with the certified No. UM.VET.2024.154 in 1/11/2024.

This study was conducted from November 2024 to May 2025. All experimental procedures were performed in accordance with the guidelines of the National Institutes of Health for the care and use of laboratory animals ("Care and Use Of," n.d.). 36 male rats at three months of age and weighing 140–200 g were employed in this experiment. Under suitable environmental conditions, these rats were maintained at a temperature of 22 ± 2 ºC, suitable humidity, and a 12-hour light-dark cycle (Salih & Al-Khashab, 2023). The animals were divided into three groups: the control group (C), which was provided with regular food, and the two experimental groups (A and D). Before beginning the trials, rats were allowed to acclimate for one week. Furthermore, the control group (12 rats) was fed a standard pelleted diet that contained 60% carbohydrates, 26% crude protein, 5% lipids, 5% crude fiber, 2% vitamin premix, and 2% mineral premix (Hussein & Mustafa, 2024). Concurrentlyfor the experimental groups, a high-fat diet (HFD) induced dyslipidemia (1.5% cholesterol, 20% lard, and 3% olive oil) added to the standard diet for eight weeks. The dyslipidemia group (24 rats) was divided into 2 groups according to the drug received by each group (atorvastatin and pitavastatin).

After induction of dyslipidemia with an 8-week HFD, as mentioned before, a blood sample was withdrawn from all groups (the control and two experimental groups) from the ocular-orbital venous plexus. These blood samples were then centrifuged at 3000 rpm for 10 minutes. The serum obtained was used to evaluate the lipid profile and PCSK9 levels using the ELISA technique, according to instructions provided by kits specific for each parameter (Lipid profile by kits provided by Biolabo, France, and PCSK9 by ELISA kit (Sunlong Biotech, China). Then, three animals from each group were sacrificed, and their liver tissues were collected to investigate the expression of PCSK9 and LDLR genes. After dyslipidemia was achieved, the dyslipidemia groups, divided into two groups, each received either atorvastatin (80 mg/kg) or pitavastatin (4 mg/kg) for 4 weeks. All drugs were administered daily by the oral route. At the end of the study (4 weeks later), other blood samples were withdrawn from all groups, and the same parameters were measured again (lipid profile and PCSK9). The animals were sacrificed, and the livers were taken from 3 animals randomly, and the same molecular tests were repeated.

To separate serum, the collected blood was centrifuged at 3000 x g for 15 minutes. *Biochemical analysis of lipids*. The profile contains TC, TG, VLDL, LDL, and HDL. They were measured by using an enzymatic colorimetric method (Biolabe, France), and concentration was determined at 500 nm by using a spectrophotometer (Vispectrophotometer, China).

Following the manufacturer's guidelines for the AddPrep Total RNA Extraction Kit (Add bio, CAS, 10119, Korea), total RNA was extracted from liver tissue using the following procedure in brief: approximately 50 mg of the designated tissue was excised and combined with the lysis buffer proteinase K solution, then mixed thoroughly using a vortex mixer. The mixture was washed many times with binding and washing buffers, and centrifuging.

The cDNA synthesis was conducted utilizing a reverse transcriptase kit and following the manufacturer's guidelines, 10 µL of AddScript RT Master (2x con.) (Addbio, Korea CAS, 22101), 7 µL of Nuclease-Free D.W., and 3 µL of RNA. The reaction mixture was prepared in a total volume of 20 µL within a 0.2 mL PCR tube. Following the preparation of the mixture, the PCR tubes were positioned in the Thermocycler (BioRad, USA), and the program was configured as detailed in Table 1.

Table 1
Temperature cycling conditions for cDNA synthesis (reverse transcriptase)

Step	Temp ℃	Time
Priming	25	10 min
Reverse transcription	60	60 min
RT inactivation	80	5 min
Hold	12	∞

Quantitative PCR was used to measure the expression levels of the PCSK9, LDLR, and GAPDH genes, utilizing particular primers as detailed in Table 2. The qPCR reaction was conducted in a 0.2 mL PCR tube with SYBR Master Mix (Addbio, Korea,70201) in a total volume of 20 µL, incorporating unique primers for each gene. The qPCR cycling parameters were established utilizing the BioRad CFX96 Real-Time PCR System (ThermoFisher, USA), as detailed in Table 3. Upon completion of amplification, the expression data were preserved for subsequent analysis.

cDNA-specific primers that had been verified were used to measure gene expression (Table 2). In the polymerase chain reaction, quantitative real-time PCR utilizes the SYBR Green master mix. RT-PCR (Addbio, Korea) using the conventional RT-PCR methodology and a Bio-Rad CFX96 real-time PCR system (ThermoFisher, USA) (Table 4). GAPDH primers serve as an internal control (housekeeping gene), with the Ct values of the RT-PCR results expressed as ΔΔCt. The results wer adjusted using the 2-ΔΔ Ct method as described by Livak (Livak & Schmittgen, 2001) and represented as fold changes in gene expression levels.

Table 2
Sequences of primers used for amplification of the GAPDH, LDL-R, and PCSK9 genes for qRT-PCR

Primer name	Primer Sequence 5' – 3'	Length	Reference	Target gene
PCSK9-F	TGGCTGCATGACATTGCTTCTC	22	Dettlaff-Pokora, 2019	Rat PCSK9
PCSK9-F	GCACTGGAGAACCACACAGG	20		
LDLR-R	ATTTTGGAGGATGAGAAGCAG	21	Ali & Ali, 2023	Rat LDLR
LDLR-R	CAGGGCGGGGAGGTGTGAGAA	21		
GAPDH-F	GCCATCAACGACCCCTTCATT	21		Rat GAPDH
GAPDH-F	CGCCTGCTTCACCACCTTCTT	21		

Results

The effect of pitavastatin on lipid profile and PCSK9 levels: Table 5 below presents a comparison between the control group and the dyslipidemic group (A) before treatment initiation. This table shows that total cholesterol (TC), triglyceride (TG), and LDL-C significantly increased in the dyslipidemic group (pre-treatment group) in comparison to the control group. In contrast, HDL-C and PCSK9 levels show insignificant changes compared to the control group. A comparison between the dyslipidemic group and the treatment group is shown in

Table 5. There was a significant decrease in TC and TG in the treatment group in comparison with the dyslipidemic group before they received pitavastatin. While PCSK9 shows a significant increase in comparison to the dyslipidemic pretreatment group. Both LDL-C and HDL-C show insignificant changes.

Table 3
Reaction mixture for qRT-PCR for amplification

Component	Volume, µL
Add SYBR Master Mix (2x conc.)	10
Nuclease-Free D.W	6
F-primer (10 µM)	1
R-primer (10 µM)	1
cDNA	2
Total	20

Note: Primers for PCSK9, LDLR and GAPDH.

The effect of atorvastatin on lipid profile and PCSK9 levels: Table 6 presents a comparison between the control group and the dyslipidemic group (B) before the initiation of treatment. The data indicate that TC, TG, and LDL-C were significantly elevated in the pre-treatment group relative to the control group. In contrast, there were no significant changes in HDL-C and PCSK9 levels when compared to the control group. Also, we see a comparison between the treatment group and the dyslipidemic post-treatment group. The treatment group's TC and LDL-C levels were significantly lower than those of the dyslipidemic group. In contrast, PCSK9 exhibits a substantial rise when compared to the dyslipidemic group. TG and HDL- both exhibit insignificant alterations.

Table 4
Cycling conditions of qRT-PCR for expression of LDL-R, PCSK9, and GAPDH genes

Step	Temp °C	Time	Cycle
Polymerase activation	95	min	1X
Denature	95	45 sec	
Annealing	*60	45 sec	35X
Extension (data collection)	72	min	
Melting analysis	60	min	1X
Dissociation (data collection)	90	0.01	1X
Hold	10	2.0	–

Note: * – annealing temperature = 60 °C was used for all studied genes.

Table 5
Comparison between the dyslipidemic group A, pitavastatin, and the control group

Parameter	Control	Dyslipidemic group pretreatment	P-value	Dyslipidemic group post-treatment (pitavastatin)	P-value
TC	87.2 ± 25.2	135.5 ± 33.6	P = 0.003*	85.6 ± 11.9	P < 0.001*
TG	49.9 ± 8.9	237.8 ± 38.2	P < 0.001*	180.5 ± 41.4	P = 0.005*
HDL	34.7 ± 5.9	41.7 ± 10.4	P = 0.053	31.1 ± 6.3	P = 0.006*
LDL-C	21.1 ± 5.8	33.5 ± 7.2	P < 0.001*	31.8 ± 3.5	P = 0.962
PCSK9	3.374 ± 1.684	2.594 ± 0.624	P = 0.201	4.012 ± 0.860	P = 0.001*

Table 6
Comparison between the dyslipidemic group B, atorvastatin, and the control group

Parameter	Control	Dyslipidemic group pretreatment	P-value	Dyslipidemic group post-treatment (atorvastatin)	P-value
TC	87.2 ± 25.2	117.6 ± 28.7	P = 0.037*	87.7 ± 8.8	P = 0.003*
TG	49.9 ± 8.9	166.1 ± 35.4	P < 0.001*	136.4 ± 21.7	P = 0.052
HDL	34.7 ± 5.9	33.5 ± 4.7	P = 0.945	40.8 ± 7.5	P = 0.110
LDL-C	21.1 ± 5.8	35.9 ± 5.7	P < 0.001*	27.9 ± 6.7	P = 0.024*
PCSK9	3.374 ± 1.684	2.425 ± 0.824	P = 0.118	5.459 ± 1.037	P < 0.001*

Comparing the PCSK9 gene expression between the control, dyslipidemic, and treatment groups reveals that pitavastatin resulted in approximately a 15-fold increase in PCSK9 expression, whereas atorvastatin resulted in an approximately 18-fold increase in gene expression compared to pretreatment values, as shown in Table 7.

Table 7
Comparison of the fold changes between the control, dyslipidemic, and treatment groups regarding PCSK9 gene expression

Liver PCSK9 expression (dyslipidemia vs. control)		Liver PCSK9 expression (dyslipidemia vs. treatment)	
animal group	fold change	animal group	fold change
Dyslipidemic (Pitava)	0.214	Treatment (Pitava)	3.226
Dyslipidemic (Atorva)	0.040	Treatment (Atorva)	0.712

Notes: Pitava – Pitavastatin, Atorva – Atorvastatin.

Comparing the LDLR gene expression between the control, dyslipidemic, and treatment groups shows that pitavastatin resulted in an approximately7-fold increase in LDLR gene expression, while atorvastatin resulted in an approximately 2-fold increase in gene expression in comparison to pretreatment values, as shown in Table 8.

Discussion

This study aimed to compare and assess the biochemical and molecular effects of pitavastatin and atorvastatin on lipid profiles and the expression of PCSK9 and LDLR genes in an induced dyslipidemic animal model. However, they showed different patterns; atorvastatin and pitavastatin both markedly improved lipid metrics. The dyslipidemic groups had significantly higher total cholesterol (TC) and triglyceride (TG) levels before therapy when compared to the control group; these findings concur with those of other researchers who reported that induced dyslipidemia is marked by a significant increase in lipid profiles, accompanied by a reduction in HDL levels (Hussein & Mustafa, 2024). This may be due to HFD's substantial enhancement of liver cholesterol and triacylglycerol. The cholesterol synthesis pathway is a complex process that necessitates approximately 25 enzymatic reactions. However, the two critical rate-limiting enzymes, hydroxyl-methyl-glutaryl-CoA reductase (HMGCR) and synthase (HMGCS), are the crucial components(Sharpe et al., 2020).

Table 8
Comparison of the fold changes between the control, dyslipidemic, and treatment groups regarding LDLR gene expression

Liver LDLR expression (dyslipidemia vs. control)		Liver LDLR expression (dyslipidemia vs. treatment)	
animal group	fold change	animal group	fold change
Dyslipidemic (Pitava)	1	Treatment (Pitava)	6.96
Dyslipidemic (Atorva)	1	Treatment (Atorva)	2.14

Note: see Table 7.

Following treatment, both statins significantly decreased total cholesterol levels, restoring them to levels near those of the control group. Nonetheless, pitavastatin demonstrated a more significant decrease in triglyceride levels than atorvastatin, indicating a possible enhanced efficacy in triglyceride reduction. Our results are in agreement with those of other researchers who have reported similar findings that compared to atorvastatin, pitavastatin was more cost-effective in lowering TGs (Poolsup et al., 2012; Devi et al., 2025). Atorvastatin causes a nonsignificant increase in HDL while pitavastatin causes a decrease in HDL, and this needs explanation. A notable drop in LDL-C was reported with atorvastatin, in agreement with other research

(Adams et al., 2012). LDL-cholesterol decreased when all the studies were combined using the dose 10 to 80 mg/day, whereas the decrease associated with pitavastatin lacked statistical significance, as we can also see with this research (Saito, 2011). This disparity may be ascribed to differences in pharmacodynamics and absorption between the two statins. HDL-C levels decreased in the pitavastatin group, and the drop was statistically more significant. This could be attributed to excessive triglyceride reduction, which modifies HDL particle remodeling, as well as alterations in lipid transfer proteins (e.g., CETP, hepatic lipase) that affect HDL homeostasis (Aydin et al., 2015). *Elevated hepatic lipase activity*: Certain statins may elevate hepatic lipase, an enzyme that hydrolyzes HDL particles, resulting in their reduction in size and enhanced clearance. This may lead to decreased HDL-C levels, despite an unchanged quantity of HDL particles or retained HDL functionality, metabolic syndrome, or inflammatory states (Welty et al., 2016; Yanai et al., 2022). In short-term trials (particularly those lasting less than six weeks), certain patients exhibited minor declines in HDL-C levels (Hasvold et al., 2016). Over time, HDL-C frequently returns or enhances as lipid metabolism normalizes, individual variability (genetics), and in people with already low triglycerides, statins may reduce VLDL production further. Less VLDL means fewer HDL precursors, potentially lowering HDL-C synthesis. Some clinical studies have shown that statins may slightly raise HDL-C (McTaggart & Jones, 2008). This is different, and more research needs to be done to find out if the benefits depend on dose or model.

Regarding the PCSK9 protein levels and gene expression, a functional sterol regulatory element (SRE) is present in the PCSK9 gene's basal regulator and is required for sterol-responsive element binding protein-2 (SREBP-2) to initiate PCSK9 transcription (Li et al., 2009). SREBP-2 controls cholesterol homeostasis in cells (Horton et al., 2002). Statins inhibit HMG-CoA reductase, leading to increased SREBP-2 activity and, paradoxically, enhanced expression of PCSK9 mRNA, which diminishes their LDL-C–lowering efficacy (Dubuc et al., 2004). This is in agreement with our molecular results and the differential modulation of PCSK9 levels by the two statins. At baseline, in the dyslipidemic state (without treatment), liver PCSK9 expression was downregulated relative to the control group, exhibiting fold changes of 0.214 for the pitavastatin group and 0.04 for the atorvastatin group. Dyslipidemia significantly suppresses PCSK9 expression in the liver, as other studies have suggested (Németh et al., 2023).

Nonetheless, post-treatment, both statins elevated circulating PCSK9 levels. Pitavastatin treatment resulted in an upregulation of liver PCSK9 expression, exhibiting a fold change of 3.226, which reflects a greater than 15-fold increase relative to the dyslipidemic state. This indicates that pitavastatin significantly enhances hepatic PCSK9 production, even in the context of dyslipidemia.

In contrast, atorvastatin treatment led to a modest increase in PCSK9 expression (fold change 0.712). Many studies have shown that elevated PCSK9 concentrations induced by pitavastatin, either alone or in combination, were observed before changes in the lipid profile in rats (Welder et al., 2010). Another study (Zhang et al., 2014) examined the time course of atorvastatin (80 mg), PCSK9, and lipid levels were measured during a 2-week period and subsequently every 4 weeks for a total duration of 16 weeks. Atorvastatin (80 mg) resulted in a rapid 47% increase in serum PCSK9 at 4 weeks, which was maintained over the 16 weeks of treatment. This corroborates the biochemical data and strengthens the idea that PCSK9 overexpression is a class effect of statins, but atorvastatin seems to have a more pronounced transcriptional activation.

In LDLR Gene Expression, the LDLR facilitates cholesterol homeostasis by binding LDL to its receptors on liver cell membranes. The ligand-binding domain is responsible for lipoprotein interaction (Fisher et al., 2004; Sithu et al., 2017). LDLR primarily facilitates the removal of LDL from circulation; therefore, a defect in this receptor, as observed in familial hypercholesterolemia (FH) in humans, leads to impaired LDL clearance (He et al., 2019).

As a result, there is an increase in the blood lipid profile. A higher lipid profile correlates with increased expression of the LDLR gene, resulting in elevated LDLR protein levels, which help mitigate hyperlipidemia. This finding is consistent with the conclusions of other researchers (Fisher et al., 2004; He et al., 2019; Sithu et al., 2017) and in agreement with our finding, because both statins elevate PCSK9 gene expression. Statins reduce cholesterol synthesis by inhibiting HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway. The reduction in cholesterol within the liver activates sterol regulatory element-binding protein-2 (SREBP-2), leading to the upregulation of low-density lipoprotein receptor (LDLR) expression and a subsequent decrease in plasma LDL-C levels. In our experiment, both statins markedly enhanced LDLR gene expression, aligning with their principal mechanism of action. Pitavastatin elicited approximately a 7-fold rise, whereas atorvastatin resulted in only a 2-fold increase, indicating a more pronounced enhancement of LDLR expression by pitavastatin, as other articles have published (Pocathikorn et al., 2010; Xu et al., 2020). This distinction is crucial, as elevated LDLR expression improves hepatic clearance of circulating LDL-C, facilitating cholesterol reduction. We can conclude Why does pitavastatin raise LDLR levels but lower LDL-C levels less.

When you compare pitavastatin to other statins, like atorvastatin or simvastatin, its pharmacokinetics and gene expression features are different; LDLR Upregulation does not necessarily mean an increase in functional activity, pitavastatin may increase LDLR expression (the number of receptors), but not all receptors are necessarily functional; some may be mislocalized, poorly recycled, or degraded quickly. So increased mRNA/protein does not always mean increased clearance (Zhang et al., 2016; Feldt et al., 2020). *LDL Particle Characteristics*, pitavastatin may alter the composition or size of LDL particles, smaller, denser LDL particles are less efficiently cleared by LDLR if pitavastatin shifts LDL to a less-clearable subtype, LDL-C won't fall as much despite LDLR increase (Choi et al., 2010; Chapman et al., 2020).

Pitavastatin highly activates SREBP-2 transcriptional pathways, even though it only slightly blocks cholesterol synthesis. This makes the LDLR gene work well, which increases the number of receptors on the membranes of hepatocytes (Saito, 2009). LDLR expression is under tight control by intracellular cholesterol and PCSK9. Even if pitavastatin upregulates LDLR, feedback mechanisms (e.g., PCSK9) can limit its effectiveness by degrading LDLRs. If pitavastatin does not suppress PCSK9 much, that may reduce the LDL-lowering effect (Mayne et al., 2008; Konrad et al., 2011), while for atorvastatin, we can see that it decreases the LDL-C significantly, but not that much in LDLR, maybe because of the activation of SREBP-2, atorvastatin increases the transcription of the LDLR gene. However, gene expression is not the only factor that determines the actual quantities of LDLR protein on the hepatocyte surface: mRNA stability, trafficking and folding of proteins, and recycling as opposed to destruction (for example, via PCSK9) (Konrad et al., 2011; Seidah & Prat, 2022).

Conclusion

Dyslipidemia is effectively induced experimentally in adult male rats using a straightforward method involving a high-fat diet over eight weeks. Treatment with both statins pitavastin and atorvastin over 4 weeks caused a valuable increase in the expression of LDLR and PCSK9 genes, where atorvastatin proved slightly more effective in increasing PCSK9 gene expression and pitavastatin more effective in increasing LDLR gene expression.

The authors declare no conflict of interest.

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