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RESEARCH ARTICLE OPEN ACCESS

Biochemical and molecular effects of atorvastatin and rosuvastatin on insulin sensitivity in rats

Effect of statins on glucose homeostasis

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Abstract
Objective: To evaluate the effects of atorvastatin and rosuvastatin on glucose regulation and insulin sensitivity in rats, focusing on biochemical, histological, and molecular changes.
Methods: Thirty male albino rats were randomised into three groups (n=10 each): control, atorvastatin (80 mg/kg), and rosuvastatin (40 mg/kg). Treatments were given orally for 30 days. Serum insulin, homeostatic model assessment of insulin resistance (HOMA-IR), oral glucose tolerance test (OGTT), and fasting blood glucose (FBG) were measured. Pancreatic tissue was examined histologically. The molecular signalling pathway was studied by measuring the gene expression of protein kinase B (AKT) and Insulin-responsive glucose transporter type 4 (GLUT4) in adipose tissue and skeletal muscle.
Results: [Atorvastatin treatment was associated with an initial reduction in fasting blood glucose and improvement in insulin sensitivity. However, by day 30, this group showed reduced glucose tolerance, increased insulin resistance, and β-cell alterations. These metabolic changes were accompanied by a transient early upregulation of AKT and GLUT4 expression in adipose tissue, which declined by the end of the study. In contrast, rosuvastatin treatment was associated with early improvement in glycaemic markers and preserved glucose tolerance, with histological changes observed in pancreatic tissue. Molecular analysis in this group showed a modest early upregulation of AKT and GLUT4 in skeletal muscle.
Conclusion: Atorvastatin and rosuvastatin exert distinct effects on glucose metabolism. While rosuvastatin showed a more stable metabolic profile, prolonged high-dose atorvastatin was associated with insulin resistance and β-cell changes.

Keywords: Atorvastatin, Rats, Rosuvastatin, Insulin resistance, Glucose homeostasis, GLUT4

Plain English Summary

Statins are vital medicines for heart health, but some may influence diabetes risk. This study found that a fat-soluble statin (atorvastatin) gradually impaired the body's sugar processing and damaged the pancreas in rats. A water-soluble statin (rosuvastatin) improved sugar levels initially but also caused pancreatic injury. This suggests that the choice of statin may be important for patients with existing diabetes risk factors.

Introduction

Heart disease, or cardiovascular disease (CVD), is among the most significant health issues, accounting for one-third of all diseases worldwide. The most prescribed medications for the treatment of hyperlipidaemia are statins (1). They are well tolerated, safe, and associated with minimal adverse effects. It is estimated that for every mmol/L of cholesterol reduction by statin therapy, there is a 22% reduction in the yearly rate of major vascular events. Emerging evidence suggests that statins have cholesterol-independent "pleiotropic" effects, such as they can improve endothelial function, increasing the stability of atherosclerotic plaques, reducing oxidative stress and inflammation, gastro gastroprotective effect (2). In addition, Statins have been shown to impact glucose regulation in several ways, including influencing β-pancreatic cells' synthesis and secretion of insulin, insulin resistance (3). As a result, the pancreas develops a compensatory mechanism for increased insulin production, which eventually causes the cells to stop responding to insulin, leading to hyperglycaemia (4, 5).

There is differentiation noted between the various forms of statins and statin dosage when discussing their diabetogenic effects (6). In addition, the use of the most popular lipophilic statin, atorvastatin, for a short period of time disrupts glucose homeostasis and inhibits LDLR expression in pancreatic islets in mice (7). While another study hypothesised that atorvastatin treatment for long-term did not affect glucose metabolism in rabbits (8), in normal diet mice, rosuvastatin was able to reduce blood glucose levels through improved insulin sensitivity and increased glucose uptake in adipose tissue. However, rosuvastatin has another effect, which is lowering insulin secretion and insulin content in islets when it was tested in vitro. As there is a controversy regarding the effect of lipophilic and

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hydrophilic statins on glucose tolerance, there is a crucial need to further investigate the effect of statins on glucose homeostasis. The study aimed to compare the molecular, biochemical and histopathological effects of hydrophilic and lipophilic statins on the glucose homeostasis after different durations of administration.

Materials and Methods

Thirty male albino rats, weighing 180--225 g, were young, aged 10--12 weeks. A 12-hour photoperiod (light/dark cycle) and a temperature of 25°C were maintained in the animals' quarters. The animals had free access to both tap water and their diet pellets.

Three groups of ten were randomly assigned to participate in this randomised controlled experimental study: Distilled water was given to Group A (control), while 80 mg/kg of atorvastatin was given to Group B; and Group C received rosuvastatin at a dose of 40 mg/kg. [Choosing the doses was due to the faster metabolism and excretion, and shorter drug half-life compared to humans, and depending on different studies in different species (9, 10, 11). All treatments were administered orally once daily for 30 days. Blood samples have been collected at the beginning of the study (day 0), on day 14, and at the end of the study (on day 30). To fulfil the study's requirements, samples of skeletal muscle, adipose tissue, and pancreas were taken on days 14 and 30.

Preparation and Administration of Atorvastatin and Rosuvastatin

Atorvastatin 40 mg tablets (Lipodar-Jordan) and rosuvastatin 20 mg tablets (Normon- Spain) were finely milled using an electric grinder to obtain a uniform powder. The resulting powder was then dissolved in distilled water (D.W.), ensuring that each 2 mL of the solution contained a concentration of 80 mg/kg of atorvastatin or 40 mg/kg of rosuvastatin. The freshly prepared solution of atorvastatin was administered orally to the animals in Group B, while the solution of rosuvastatin was administered to Group C using a tip-ball gavage syringe.

Collection of blood and tissue samples

A capillary tube was used to quickly puncture each rat's retroorbital plexus to extract blood from each animal. Clean 1.5 ml Eppendorf tubes were used to transfer and separate the clear sera into aliquots, which were then kept at -20°C for the subsequent examination of glucose intolerance, such as fasting blood glucose level, insulin, and HOMA-IR parameters.

Biochemical Tests

Fasting serum glucose

The enzymatic reference technique, using glucose oxidase, was employed to quantify serum glucose with a colourimeter. At 500--520 nm, the absorbance of the coloured complex is determined in proportion to the amount of glucose present in the specimen.

Insulin

Rat Insulin ELISA Kit (SL0373Ra, Sunlong, China) is used to measure insulin levels in rat serum and according to the instructions of the manufacturer. Insulin was detected colourimetrically using a Horseradish peroxidase (HRP)-conjugated secondary antibody with Chromogen Solution (A and B) as substrate. The optical density (OD) is measured spectrophotometrically at 450 nm, and the OD value is proportional to the concentration of insulin in the samples. The concentration of insulin in the samples is determined by comparing the OD of the samples to the standard curve.

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)

The HOMA method assesses insulin resistance and beta-cell activity by using mathematical modelling with fasting plasma glucose and insulin levels from blood samples. The HOMA-IR equation is as follows:

HOMA−IR= Fasting Glucose (mmol/l) ×(Fasting Insulin (mIU/l)) / 22.5

Oral glucose tolerance test

The thirty rats (control, atorvastatin, and rosuvastatin) were subjected to an overnight fast of 19 hours before the test, with unlimited access to water. After that, they have been given a glucose solution (1.5 g/kg) via oral gavage syringe. Each rat received 2 ml of the glucose solution, which was made by dissolving ten grams of five per cent D-glucose in 50 ml of sterile water. Blood glucose levels were measured before glucose administration (at time 0) and at 30-, 60-, 90-, and 120-minute post-glucose administration. Blood samples were collected from the tail vein using sterile techniques and were analysed using an Accu-Chek meter.

Histopathological assessment

After tissue samples were collected, the tissue fixation process was started by immersing them for at least 72 hours in a 10% neutral buffered formalin solution. All tissue samples were stained with haematoxylin and eosin. For each specimen, two slides were evaluated using a colour USB 2.0 digital image (HDMC) camera and image processing software (Scope Image 9.0-China) (12, 13). The sections were examined for different forms of pancreatic damage, including necrosis of pancreatic acini, pancreatic cyst, congested blood vessels, oedema, the pancreas invested with large amounts of adipose tissue, and infiltration of inflammatory cells.

Measurement of GLUT4 and Akt Gene expression by Real Time-PCR

Total RNA was isolated from adipose tissue and skeletal muscle utilising the AddPrep Total RNA Extraction Kit, which combines a spin column-based technique with DNase I treatment to eradicate genomic DNA contamination. Following the homogenization and lysis of 100 mg tissue samples, RNA was purified and eluted for subsequent applications. The RNA content and purity were assessed with a NanoDrop One spectrophotometer, and samples were diluted to a final concentration of 25 ng/µl employing the standard dilution equation. For cDNA synthesis, 10 µl of RNA was combined with 10 µl of reverse transcriptase enzyme and incubated in a thermal cycler for 75 minutes. The PCR reaction mixture comprised 2 µl of cDNA, 10 µl of RealQ Plus 2× Master Mix, 1 µl each of forward and reverse primers, and 6 µl of PCR-grade water. Gene amplification was conducted utilising the StepOne Real-Time PCR system under the following cycling parameters: initial denaturation at 95 °C for 15 minutes, followed by 40 cycles comprising denaturation at 95 °C for 30 seconds, annealing at 60 °C for 30 seconds, and extension at 72 °C for 30 seconds. Gene-specific primers were

employed for GLUT4, AKT, and β-actin, the last serving as a housekeeping gene. Sequences of primers are present in Table 1.

Table 1: Sequences of primers

ID gene	Sense sequence (5' to 3')	Tm
GLUT4-F	5'-GAAACGGAAGTTGGAAAGA-3'(19mer)	55.5
GLUT4-R	5'-CTACTAAGAGCACCGAGACC-3'(20mer)	59.1
AKT-F	5'-GAGGAGCGGGAAGAGTG-3'(17mer)	61.7
AKT-R	5'-GAGACAGGTGGAAGAAGAGC-3'(20mer)	60.7
2B-ACTIN-F	5'-GCCAACCGTGAAAAGATG-3'(18mer)	56.6
2B-ACTIN-R	5'-CCAGGATAGAGCCACCAAT-3'(19mer)	59.5

Statistical Analysis

The statistical program GraphPad Prism was used to produce analytical statistics. The data were presented as mean ± Standard Error of Mean (SEM). A one-way ANOVA test was used to compare the mean differences of one variable between three groups, whilst a two-way ANOVA test was used to compare the mean differences of two variables in the OGTT test. This is followed by post hoc Dunnett's test. The levels of gene expression were compared using A one-way ANOVA with Tukey's post hoc test. A P-value of less than 0.05 was considered statistically significant.

Results

Fasting blood glucose levels

The effect of atorvastatin and rosuvastatin on FBG is investigated. After 2 weeks, both atorvastatin and rosuvastatin caused a significant reduction ($p < 0.001$) in FBG compared to the control group. However, there was no difference in FBG between the control, atorvastatin, and rosuvastatin groups after 4 weeks (Figure 1).

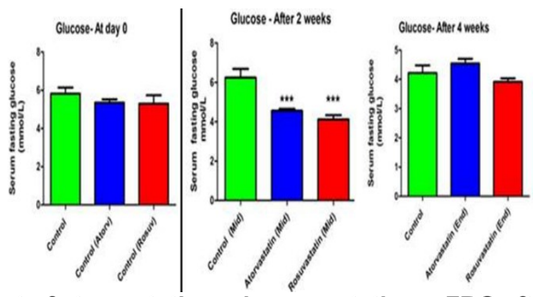

Figure 1: The effect of atorvastatin and rosuvastatin on FBG after 2 and 4 weeks.
FBG levels are evaluated following an oral atorvastatin dose of 80 mg/kg and an oral rosuvastatin dose of 40mg/kg for 2 and 4 weeks. The data are presented as mean ± SEM. *** indicates $p<0.001$. A one-way ANOVA with Dunnett's post hoc test was used. (n=10 for each group after 2 weeks, and n=7 for each group after 4 weeks)

Serum insulin levels

Regarding the levels of serum insulin, there was no effect of either atorvastatin or rosuvastatin on serum insulin levels after 2 weeks. In contrast, atorvastatin could increase serum insulin significantly ($p < 0.001$) after 4 weeks, while rosuvastatin did not affect the insulin level ([Figure 2]{.mark}).

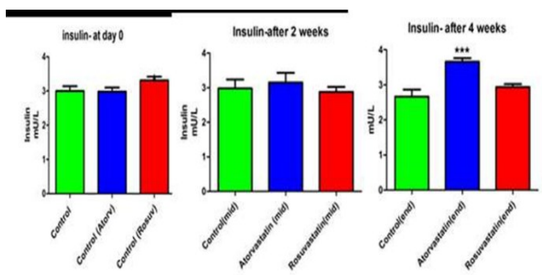

Figure 2: The effect of atorvastatin and rosuvastatin on serum insulin levels after 2 and 4 weeks
Serum insulin levels are evaluated following an oral atorvastatin dose of 80 mg/kg and an oral rosuvastatin dose of 40mg/kg for 2 and 4 weeks. The data are shown as mean ± SEM. *** denotes $p<0.001$. Dennett's post hoc test in conjunction with a one-way ANOVA was applied. (n=10 for each group after 2 weeks, and n=7 for each group after 4 weeks)

HOMA-IR measurements

The measurement of HOMA-IR indicated that the rosuvastatin group had significantly lower levels of [HOMA-IR] compared to the control group ($p < 0.05$) after 2 weeks, while the atorvastatin group showed a non-significant reduction in the [HOMA-IR]. However, after 4 weeks, [HOMA-IR]{.mark} in the atorvastatin group was significantly higher ($p < 0.001$) than that in the control and atorvastatin groups (Figure 3).

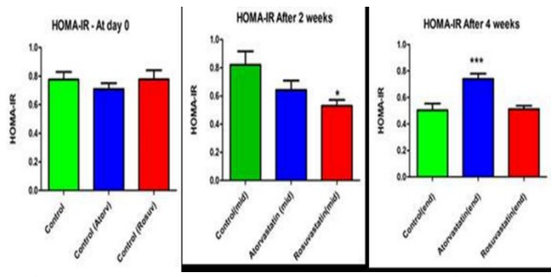

Figure 3: The effect of atorvastatin and rosuvastatin on HOMA-IR after 2 and 4 weeks
HOMA-IR is evaluated following oral atorvastatin dose of 80 mg/kg and oral rosuvastatin dose of 40mg/kg for 2 and 4 weeks. The mean ± SEM is used to display the data. *** means p is less than 0.001. Dunnett's post hoc test in conjunction with a one-way ANOVA was employed. (n=10 for each group after 2 weeks, and n=7 for each group after 4 weeks)

Oral Glucose Tolerance Test (OGTT)
After 14 days, an OGTT was performed on all rats by measuring blood glucose levels after administration of glucose (1.5 g/kg) at 0, 30, 60, 90 and 120 min. In comparison with the control, both the atorvastatin and the rosuvastatin groups showed a significantly lower blood glucose level at 30 min. However, only the atorvastatin group showed a significant impairment in glucose clearance, with blood glucose levels remaining elevated compared to control in the following time intervals (60, 90, 120 min) (Figure 4). In contrast, OGTT at the end of the experiment on day 30 showed no significant effect of either rosuvastatin or atorvastatin on the glucose tolerance in comparison with the control (Figure 5).

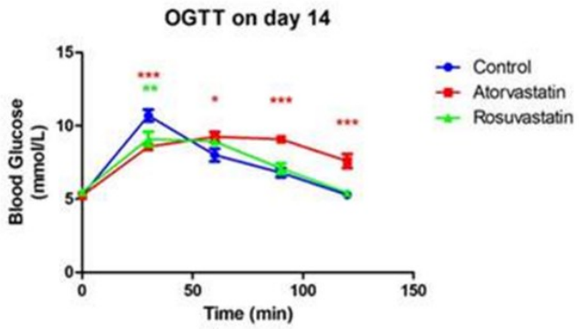

Figure 4: OGTT results in control, atorvastatin, and rosuvastatin rats on day 14
After taking 1.5 g/kg of oral glucose, blood glucose levels were assessed at 0, 30, 60, 90, and 120 minutes. The mean ± SEM is used to display the data. ** denotes p<0.01, *** denotes p<0.001, and * denotes p<0.05. Dunnett's post hoc test was employed in conjunction with a two-way ANOVA. (n=10 for each group)

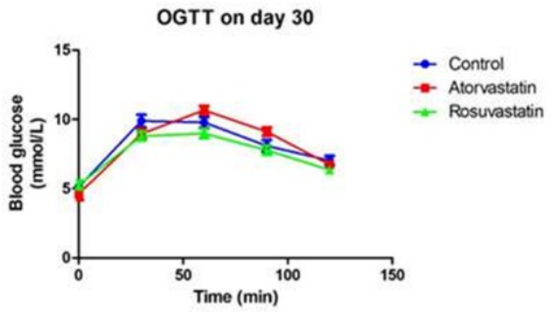

Figure 5. OGTT results in control, atorvastatin, and rosuvastatin rats on day 30
After taking 1.5 g/kg of oral glucose, blood glucose levels were assessed at 0, 30, 60, 90, and 120 minutes. The data is displayed as mean ± SEM. Dunnett's post hoc test was employed in conjunction with a two-way ANOVA. ($p < 0.05$, n=7 for each group)

Measurement of Gene Expression of AKT and GLUT4
The effect of atorvastatin and rosuvastatin on adipose tissue
After 2 weeks, there was no significant change in the expression of both AKT and GLUT4 by atorvastatin and rosuvastatin in adipose tissue. Atorvastatin caused a significant increase in gene expression of GLUT4 in comparison with rosuvastatin. After 4 weeks, there was an enhancement of GLUT4 and AKT expressions by rosuvastatin compared to atorvastatin (Figure 6).

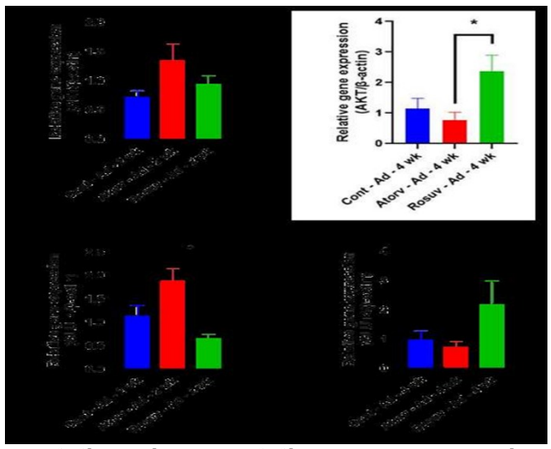

Figure 6: Effect of atorvastatin and rosuvastatin on gene expression of AKT and GLUT4 in adipose tissue

Gene expression levels were quantified via real-time PCR and standardised against β-actin. (A) Relative expression of AKT following two weeks. (B) Relative expression of AKT following 4 weeks. (C) Relative expression of GLUT4 following two weeks. (D) Relative expression of GLUT4 following 4 weeks. Data are expressed as mean ± SEM. * denotes statistically significant differences ($p < 0.05$). A One-way ANOVA with Tukey's post hoc test was used. (n=6 for each group)

The effect of atorvastatin and rosuvastatin on skeletal muscle

After 2 and 4 weeks, there was no effect on the expression of genes in skeletal muscle by either atorvastatin or rosuvastatin (Figure 7).

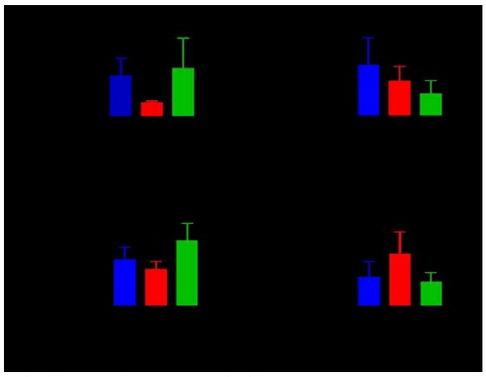

Figure 7: Effect of atorvastatin and rosuvastatin on gene expression of AKT and GLUT4 in skeletal muscle

Gene expression levels were quantified via real-time PCR and standardised against β-actin. (A) Relative expression of AKT following two weeks. (B) Relative expression of AKT following 4 weeks. (C) Relative expression of GLUT4 following two weeks. (D) Relative expression of GLUT4 following 4 weeks. Data are expressed as mean ± SEM. No significant differences were observed ($p > 0.05$). A One-way ANOVA with Tukey's post hoc test was used. (n=6 for each group)

Histopathological Results of Pancreas

Control group

Under the light microscope, the pancreatic section of the control group exhibited a typical pancreas histology with normal histological structure represented by normal architecture of pancreatic tissue, islets of Langerhans, and interlobular septa of connective tissue (Figure 8).

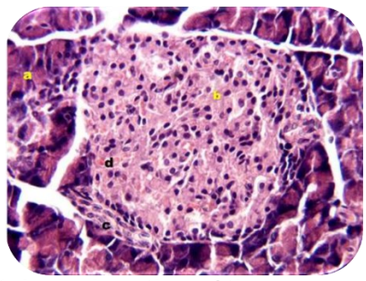

Figure 8: Representative histological section of the pancreas of the control group in rats

Control group shows normal architecture of pancreatic tissue: (a) pancreatic acini, (b) islet of Langerhans, (c) interlobular duct, (d) blood vessel. H&E. (100x; B- 400x)

The atorvastatin group after two weeks

Under the light microscope, the pancreatic section of the rat, which has been given atorvastatin for 2 weeks, showed histological changes represented by mild degeneration in the periphery of islets of Langerhans, fibrosis, congested blood vessels, and inflammatory cell infiltration (Figure 9).

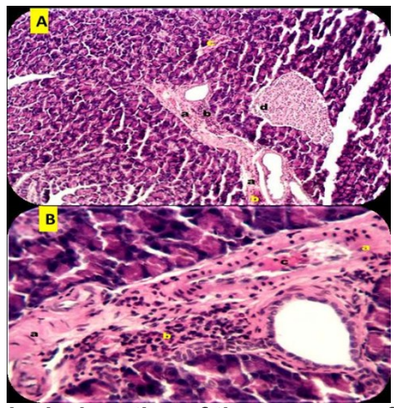

Figure 9: Representative histological section of the pancreas of the atorvastatin group in rats
The atorvastatin group shows (a) fibrosis, (b) infiltration of inflammatory cells, (c) congested blood vessels, and (d) mild degeneration in the periphery of islets of Langerhans. H&E. (A-100x; B- 400x)

The Rosuvastatin group after two weeks
The pancreatic section of the rosuvastatin under the microscope demonstrated necrosis of islets of Langerhans and invasion by pancreatic acini, congested blood vessels, fibrosis, vacuolar degeneration, and apoptotic cells (Figure 10).

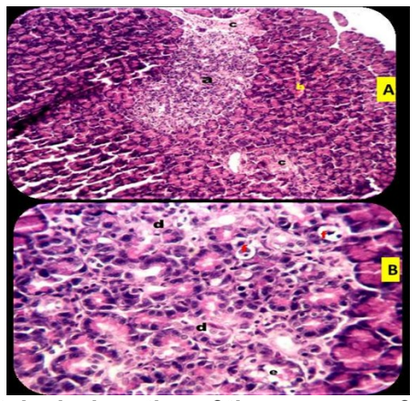

Figure 10: Representative histological section of the pancreas of the rosuvastatin group in rats
The Rosuvastatin group shows (a) necrosis of islets of Langerhans and invasion with pancreatic acini, (b) congested blood vessels, (c) fibrosis, (d) necrosis of islets of Langerhans and invasion with pancreatic acini, (e) vacuolar degeneration, (f) apoptotic cells. H&E. (A-100x; B- 400x)

The atorvastatin group after four weeks
Histological section of pancreatic tissues for rats taking oral atorvastatin for 4 weeks showed necrosis of pancreatic acini, pancreatic cysts, congested blood vessels, and oedema, as shown in Figure 11).

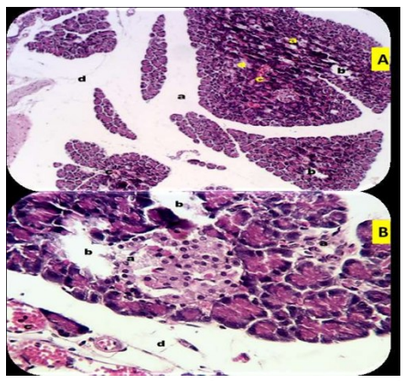

Figure 11: Representative histological section of the pancreas of the atorvastatin group in rats.
The Atorvastatin group shows (a) necrosis of pancreatic acini, (b) pancreatic cyst, (c) congested blood vessel, and (d) oedema. H&E. (A-100x; B- 400x)

The Rosuvastatin group after four weeks
The histological section of the pancreas of a rat that has been given rosuvastatin for four weeks showed oedema, congested blood vessels, and the pancreas invested with large amounts of adipose tissue, as shown in Figure 12.

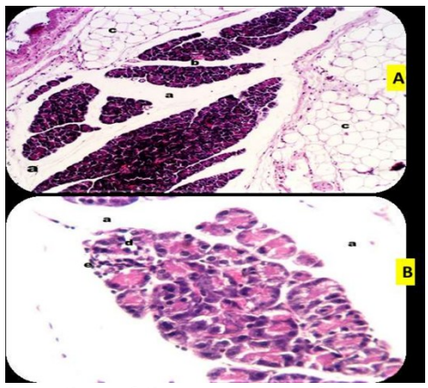

Figure 12. Histological section of the pancreas of the rosuvastatin group in rats
The Rosuvastatin group shows (a) oedema, (b) congested blood vessels, (c) the pancreas invested with large amounts of adipose tissue, (d) vacuolar degeneration of acini, (e) infiltration of inflammatory cells. H&E. (A-100x; B- 400x)

Discussion

Statins are very successful in preventing CVD in those with or without diabetes mellitus (14). However, numerous studies suggest a link between statin therapy and newly diagnosed diabetes (15, 16). Research suggests statin medication causes increased insulin resistance (17). While some research revealed that statins do not affect insulin sensitivity (18, 19). The Fremantle Diabetes Study, an observational study in Australia, found that low-intensity statins were not associated with any change in haemoglobin A1c. However, moderate-intensity statins were associated with a mean increase of 0.22% (P = 0.022), and high-intensity statins were associated with a mean increase of 1.05% (P = 0.023) (20). These findings suggest that while atorvastatin may have a neutral or slightly favourable effect on fasting glucose metabolism, it may concurrently impair dynamic glucose homeostasis, possibly through mild pancreatic dysfunction or peripheral insulin resistance. These findings are in line with other research, which found that atorvastatin administration can reduce glucose uptake and disrupt insulin signalling in skeletal muscle cells, potentially leading to negative metabolic consequences (21). Baker et al. (2010) found that atorvastatin has adverse effects on glucose metabolism and is considered the most adverse diabetogenic statin (22). Another research revealed that atorvastatin can also alter pancreatic islet cells, which can lead to a state resembling insulin resistance and altered glucose homeostasis (23). In addition, the high dose of atorvastatin used in the present study could be behind this deteriorating effect. Most studies and clinical investigations demonstrated that high-dose atorvastatin (80 mg\day) increased the incidence of new onset diabetes more than lesser doses (24, 25). A slightly increased incidence of new onset of diabetes was linked to atorvastatin at moderate dosage. A clinical research study demonstrated a risk ratio of 1:10 for people taking atorvastatin 10 mg vs 80 mg (26). Regarding the present molecular findings, another study showed that the GLUT4 protein was significantly elevated in subcutaneous adipose tissue of obese mice produced by monosodium glutamate and treated with atorvastatin, which was accompanied by an improvement in whole-body insulin sensitivity (27). In line with this study, Chen et al. (2024) have also demonstrated that atorvastatin therapy could reduce the phosphorylation of AKT in differentiated L6 skeletal muscle cells (21). Moreover, AKT exhibited a substantial reduction in activity in human skeletal muscle myotubes treated with statins for both short-term periods of 96 hours and prolonged durations exceeding 6 months (28). In addition, atorvastatin impaired GLUT4 translocation to the plasma membrane, hence altering glucose clearance in muscle and adipose tissues (29).

The dose of atorvastatin used in rats is roughly equivalent to high-intensity human therapy (≈80 mg/day), which is known to carry a higher risk of new-onset diabetes. While rosuvastatin is generally considered metabolically safer due to its hydrophilicity, our findings suggest it may still cause pancreatic injury. In humans, those with obesity, metabolic syndrome, or reduced β-cell reserve are at greater risk of statin-induced dysglycaemia. Thus, careful monitoring of glucose and weight is recommended during high-dose statin therapy, while balancing these risks against the clear cardiovascular benefits.

Study Limitations

A limitation of the study is the relatively small sample size, which needs further confirmation by other larger-scale studies. In addition, protein-level validation (e.g., Western blot) for AKT and GLUT4 is highly recommended to support mRNA findings.

Conclusion

This study demonstrates that atorvastatin and rosuvastatin have distinct, tissue- and time-dependent impacts on insulin signalling pathways, likely influenced by their varying lipophilicity. Atorvastatin, a lipophilic statin, is associated with a progressive decline in insulin sensitivity and pancreatic integrity. Although it initially upregulated insulin signalling markers such as AKT and GLUT4 in adipose tissue, these effects diminished over time, coinciding with elevated insulin levels and increased HOMA-IR, indicative of systemic insulin resistance. Conversely, rosuvastatin, a hydrophilic statin, elicited transient improvements in fasting glucose and HOMA-IR, the effect of which is likely mediated through mechanisms independent of direct gene regulation, with a delayed and modest upregulation of AKT and GLUT4 expression in adipose tissue. This may reflect a compensatory attempt to preserve glucose homeostasis despite underlying pancreatic damage. Overall, the findings underscore that the metabolic impact of statins extends beyond lipid regulation, and their long-term use, particularly at high doses, requires caution in individuals susceptible to insulin resistance.

List of Abbreviations

AKT: Protein kinase B
CVD: Cardiovascular disease
FBG: Fasting blood glucose
GLUT4: Glucose transporter type 4
HOMA-IR: Homeostatic model assessment of insulin resistance
IR: Insulin resistance
OGTT: Oral glucose tolerance test
ROS: Reactive oxygen species
T2DM: Type 2 diabetes mellitus

Declarations

Ethical approval and consent to participate

The study was conducted with approval from the Institutional Animal Care and Use Committee of the University of Mosul's College of Veterinary Medicine in Iraq. Ref: UM.VET.2024.096.

Consent for publication

All authors have approved the manuscript and agree with its submission

Availability of data and materials

The data are available upon reasonable request.

Competing interest

There are no competing interests.

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Authors' contributions

AH designed the study, while MDW performed the experiments. MDW wrote the draft of the manuscript. Both authors revised the manuscript and approved the final version.

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