



Gene expression of LDLR, APOB, APOE, and LPL in experimentally induced diabetes and dyslipidemia in rats

H.S. Mahmood¹ , N.G. Mustafa² 

¹M.Sc. Student in Veterinary Biochemistry, ²Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Mosul, Mosul, Iraq

Article information

Article history:

Received May 1, 2025

Accepted October 2, 2025

Published July 5, 2026

Keywords:

Diabetes

Dyslipidemia

Gene Expression

LDLR

LPL

Correspondence:

N.G. Mustafa

nashaat74@uomosul.edu.iq

Abstract

Diabetes is the predominant metabolic condition in humans and animals, particularly in pets; it frequently coexists with many other metabolic abnormalities involving carbohydrates, proteins, and lipids. This study was conducted to investigate the correlation between experimentally generated diabetes and dyslipidemia concerning the gene expression of low-density lipoprotein receptor (LDLR), apolipoprotein-B (APOB), apolipoprotein-E (APOE), and lipoprotein lipase (LPL) in adipose tissue. Sixty-four adult male albino rats were divided into four groups: the first group (control group), receiving a standard diet, while the second group became the dyslipidemia group, which was fed accordingly high-fat diet (HFD), the third group was the diabetes and dyslipidemia group or mixed group fed HFD. Taking a single dosage of 50 mg/kg of streptozotocin (STZ) intraperitoneally, the fourth group became the diabetic group. fed a standard diet and using a single-dose of 50 mg/kg STZ. Results demonstrated that diabetes and dyslipidemia cause significant changes in lipid profile, insulin resistance, and body weight parameters. Dyslipidemia exhibited a significant elevation in total cholesterol and triglycerides relative to the control group. STZ caused a notable elevation in glucose levels and a reduction in insulin levels, those changes resulted in upregulation or downregulation in gene expression of LPL, LDLR, APOB, and APOE. LPL gene expression is downregulated except in the diabetes group, which is slightly upregulated. LDLR gene expression significantly increased in dyslipidemia. It could be concluded that the coexistence of diabetes and dyslipidemia worsens most biochemical markers and gene expression, appearing to be more synergistically harmful than either condition alone.

DOI: [10.33899/ijvs.2025.159710.4269](https://doi.org/10.33899/ijvs.2025.159710.4269), ©Authors, 2026, College of Veterinary Medicine, University of Mosul.

This is an open access article under the CC BY 4.0 license (<http://creativecommons.org/licenses/by/4.0/>).

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder defined by elevated blood glucose levels, which arise from inadequate insulin production in Type 1 diabetes or from impaired insulin utilization in Type 2 diabetes, commonly associated with insulin resistance (1,2). On the other hand, dyslipidemia is marked by raised levels of total cholesterol, low-density lipoprotein cholesterol (LDL-c), and

triglycerides, or decreased levels of high-density lipoprotein cholesterol (HDL-c). Dyslipidemia has become recognized as a significant risk factor of cardiovascular disease (3). Diabetic Dyslipidemia refers to a collection of irregularities in lipoprotein levels, defined by qualitative as well as quantitative alterations in lipids and lipoproteins. This includes elevated triglyceride levels, reduced HDL, and an increase in LDL. This condition is widespread in individuals with type II diabetes, Influencing approximately 70 percent

of the patients (4). The resistance to insulin impairs lipid metabolism via influencing the activity of enzymes, including cholesteryl ester transfer protein along with lipoprotein lipase, is associated with the underlying cause (5). Genetic predisposition, obesity, physical inactivity, poor glycemic control, and lifestyle choices, including alcohol consumption, all contribute to the development of diabetic dyslipidemia through various risk factors (6,7). On the other hand, the LDL receptor (LDLR) gene is crucial for the regulation of cholesterol levels in the body (8,9). The LDLR pathway functions as a negative feedback mechanism crucial for the control of plasma and intracellular cholesterol homeostasis (10). Both cholesterol and triacylglycerol circulate within the hydrophobic part of lipoprotein particles, which are isolated and protected from the aqueous environment of blood plasma by outward-facing apolipoproteins and phospholipids. Whereas lipoproteins, as a type of plasma protein, are classified into several categories: chylomicrons (CM), very low-density lipoproteins (VLDL), LDL, intermediate-density lipoproteins (IDL), and HDL. These classes are distinguished by their size, density, function, lipid and protein composition, and their specific apolipoprotein content. Interestingly, apolipoproteins help maintain the stability of these lipoprotein particles, serve as ligands for their specific receptors, and act as cofactors for various handling and transport processes (11). The principal apolipoproteins that govern lipoprotein metabolism are apolipoprotein B-100 (apoB-100), apolipoprotein B-48 (apoB-48), apolipoprotein A-I (apoA-I), apolipoprotein C-II (apoC-II), apolipoprotein C-III (apoC-III), apolipoprotein E (apoE), and apolipoprotein(a) (apo(a)), ApoB-100 functions as the principal structural element of VLDL, IDL, LDL, and lipoprotein (a) (Lp(a)) (12). ApoB-48 is a shortened variant of apoB-100 and serves as the unique marker for intestinal chylomicrons; it cannot be transferred across lipoproteins as apoB-100 can (13). ApoA-I is the principal constituent of HDL particles and is essential for reverse cholesterol transfer, while ApoC-II, apoC-III, and apoE participate in the metabolism of triglyceride-rich lipoproteins. Apo(a) covalently attaches to apoB-100 inside the Lp(a) particle (14,15). Lipoprotein lipase (LPL) is an essential enzyme in humans that supplies energy to peripheral tissues. LPL hydrolyzes triglycerides from the cores of circulating lipoproteins in plasma and engages with receptors to facilitate lipoprotein absorption, hence regulating lipid distribution through both catalytic and non-catalytic mechanisms (16). The aim of this study was to evaluate the gene expression patterns of LDLR, APOB, APOE, and LPL genes that considerably linked to the diabetes and dyslipidemia.

Materials and methods

Ethical approval

The ethical committee of the Institutional Animal Care Committee of the College of Veterinary Medicine, University of Mosul, Iraq, approved permission for this work, under certification number UM.VET.2024.009.

Animals

This project comprised sixty-four male adult albino rats, aged two to three months and weighed 200 to 240 grams. All experimental techniques were executed in compliance with the National Institutes of Health (NIH) (17) standards for the care and use of lab animals and received approval from the laboratory animal care committee of the College of Veterinary Medicine/ University of Mosul. The experimental works were done in the College of Veterinary Medicine/ University of Mosul during September 2024 to April 2025. For 45 days animals had maintained in adequate environmental conditions, comprising an average temperature of 22 ± 2 °C, suitable for humid conditions, and a 12-hour light/dark cycle (18-20).

Experimental design

Animals were divided into four groups; Control Group (Group A), had fifteen adult male rats who were given a standard diet for 45 days without any supplementary drugs. Dyslipidemia Group (Group B), comprised fifteen male adult rats that were fed a high-fat diet (HFD) for 45 days, without introducing any other chemicals (18,20). Diabetic and Dyslipidemia Group (Mixed Group or Group C), included seventeen male adult rats (Due to STZ-related mortality, the number of rats in groups C and D was seventeen instead of fifteen) that received a high-fat diet (HFD) for 45 days, along with streptozotocin (STZ) at a single dosage of 50 mg/kg via an intraperitoneal (IP) injection (21). Out of 34 rats injected with STZ from groups C and D, only eight required a second dose of STZ. Diabetic Group (Group D), consisted of seventeen adult male rats that were given a standard diet for 45 days and then given STZ (dissolved in sodium phosphate buffer solution) and given at a single dose of 50 mg/kg via an intraperitoneally (IP) (21).

Streptozotocin (STZ)

The STZ [2-deoxy-2-(3-methyl-3-nitrosourea)-1-D-glucopyranose] (CAS No. 18883-66-4) (22). An antimicrobial produced by *Streptomyces achromogenes* is among the most often utilized diabetogenic drugs due to its low cost and little adverse effects (23-25). The mechanism of STZ induces death of β -cells of the pancreatic islet and is extensively utilized in experimental settings to create a model of type 1 diabetes mellitus and type II diabetes mellitus when paired with nicotinamide (NA) (26,27). The STZ used was sourced from BLD Pharmatech in China.

High-Fat Diet (HFD)

The HFD had been used to cause dyslipidemia in groups B and C. The HFD was prepared using 1.5% cholesterol, 3% olive oil, and 17% butter (20,28,29) added to a standard diet. It had been given to groups B and C of rats for a period of 45 days.

Biochemical tests

At the end of the experiment, a heparinized capillary tube was used to collect blood from the retro-ocular vein of every rat. The obtained blood was subsequently centrifuged at 3,000 x g for 15 minutes for separating the serum (30,31). The serum was subsequently preserved at -20 °C for biochemical examination. (32). Serum insulin level was measured employing a sandwich ELISA kit (Ideal, China) (CAT No. ER1113). formulated for rats (33), using a microplate reader, absorbance measurements taken at 450 nm (Biotek, USA). Serum glucose concentrations were assessed with an enzymatic approach (oxidase-peroxidase) utilizing a kit (Giesse, Italy) (CAT No. 4057), with measurements taken at 505 nm using a chemical analyzer (Smart 120, USA). Insulin resistance was evaluated by HOMA-IR as follows: $\text{HOMA-IR} = \text{Fasting insulin } (\mu\text{U/ml}) \times \text{Fasting glucose } (\text{mmol/L}) / 22.5$ (34). Serum lipid profile, including serum total-cholesterol (TC), triacylglycerol (TG), LDL-cholesterol, HDL-cholesterol, and VLDL-cholesterol were quantified using an enzymatic colorimetric technique (35,36) using a Giesse (Italy) kit (CAT No. REF 1001/12). The concentrations were determined at a wavelength of 500 nm by a Smart 120 chemical analyzer from the (USA). that was done in HPLC lab/ Mosul city/Iraq.

mRNA isolation and RT-PCR

The following steps were performed to isolate mRNA from the adipose tissue: a 25-50 mg tissue sample was ground into liquid nitrogen using a mortar. This powder was then mixed with 1 ml of Trizol (GDSBio, China), then RNA extraction is done by the FavorPrep blood/cultured cell Total-RNA purification kit (FavorgenBiotech, Taiwan) (CAT No. FABRK. 001-1). the Nanodrop 2000/2000c (Thermo-Fisher Scientific, USA) was employed to determine mRNA amount. The reverse transcriptase kit (GDSBio, China) cDNA was synthesized following the manufacturer's guidelines, using the Techne Te 312 (Barloworld Scientific, UK). The temperature cycling protocol of Reverse Transcription is shown in Table 1. Gene expression was assessed via quantitative real-time polymerase chain reaction (RT-PCR) employing established methods. cDNA-specific primers by BlasTaq™ 2X qPCR Master mix SYBR Green (BlasTaq™ 2X qPCR Master Mix, Canada) (Cat. No. G891). The primer sequence of the reference gene, LDLR gene, and ApoB gene had been previously published by Hussein and Mustafa (20), ApoE gene by Liu *et al* (34), and of LPL gene by Liang *et al*. (38)

(Table 2). DNA amplification was conducted according to the standard protocol of RT-PCR employing the PowerAmp96™ Dx RT-PCR machine (Kogenebiotech, South Korea) (Table 3). The Ct values from RT-PCR data were presented as $\Delta\Delta\text{Ct}$ and normalized using the $2^{-\Delta\Delta\text{Ct}}$ approach as defined by Livak's method (37), reflecting variations in gene expression levels. Primers for GAPDH, utilized as an internal control (housekeeping gene), were used.

Table 1: The temperature cycling Protocol of Reverse Transcription

Steps	Temperature (°C)	Time
Reverse transcription	50°C	15 min
RT inactivation	85°C	5 sec
Hold	4°C	∞

Table 2: Primer Sequences for housekeeping gene (GAPDH) and target genes

Gene	Primer
GAPDH	F 5'-GCCATCAACGACCCCTTCATT-3'
	R 5'-CGCCTGCTTCACCACCTTCTT-3'
LDLR	F 5'-ATTTTGGAGGATGAGAAGCAG-3'
	R 5'-CAGGGCGGGGAGGTGTGAGAA-3'
ApoB	F 5'-GAAAGCATGCTGAAAACAACC-3'
	R 5'-AGGCCTGACTCGTGGAAGAA-3'
ApoE	F 5'-TGTTGGTCCCATTGCTGACAGGAT-3'
	R 5'-TGGTGTTCCTCGTTGCGGTACT-3'
LPL	F 5'-ATGGTTTCTTCTTGGTGG-3'
	F 5'-TCAGTGCTTCTCCAGAGTTAC-3'

Table 3: The cycling protocol was programmed according to the thermal profile below

Step	Temperature	Duration	Cycles
Enzyme activation	95°C	3 min	Hold
Denaturation	95°C	15 sec	40
Annealing/extension	60°C	1 min	
	95°C	1 min	
Melting	60°C	15 sec	1 Cycle
	98°C	5 sec	

Statistical Analysis

The data was expressed as a mean $\pm$ standard deviation (SD). A one-way analysis of variance (ANOVA) was employed to assess the values. A P-value of $p \leq 0.05$ was utilized to assess the significance of the differences. The study was conducted using SigmaPlot software, Version 15 (38).

Results

DM was successfully developed in rats using STZ, a single dose of 50 mg/kg within 45 days (Table 4). There is a significant elevation in glucose and an acceptable reduction in insulin. Also, there were a significant change in insulin resistance (HOMA-IR) (Table 4). While dyslipidemia was acceptably induced in rats by HFD within 45 days (Table 4). HFD can raise LDL-cholesterol levels. That is a key marker of dyslipidemia. In a study on Sprague Dawley rats, a HFD led to markedly elevated blood LDL levels in comparison to controls, despite no significant difference in body weight, indicating that dyslipidemia can occur independently of obesity. There is a significant elevation of TCs, TG, and also there are increase in VLDL, and LDL, and slight reduction in HDL (Table 5).

However, mRNA was extracted, and its purity was assessed and validated using a Nanodrop spectrophotometer. Following the conversion of mRNA to cDNA, the cDNA was amplified by RT-PCR, and the expression levels of the LDLR and ApoB genes were quantified as fold changes relative to the housekeeping gene GAPDH. Dyslipidemia corresponds with downregulation of LPL gene and upregulation of LDLR, APOB, and APOE gene as a compensatory strategy to combat high lipid levels. While

diabetes corresponded with a lower level of upregulation compared to dyslipidemia. While in the diabetes and dyslipidemia group LPL and LDLR gene expression are down regulate in the same time APOB and APOE are upregulated. In comparison to Group A, Group B exhibited marked upregulation of LDLR (5.9-fold), ApoB (5.5-fold), and ApoE (3.8-fold), alongside severe suppression of LPL (0.28-fold) compared to the control group. Group C showed partial attenuation of these effects, with LDLR reduced to 0.46-fold and LPL slightly improved (0.31-fold), though ApoB (3.45-fold) and ApoE (2.02-fold) remained elevated compared to the control group. Group D displayed a distinct profile, combining moderate upregulation of LPL (1.61-fold) and LDLR (1.94-fold) with persistently high ApoB (3.97-fold) and ApoE (1.76-fold) compared to the control group. Notably, GAPDH expression remained relatively stable across groups (1.1–1.26-fold changes), though its slight increase in Group D (1.26-fold) may warrant caution if used for normalization. These fold changes suggest divergent regulatory mechanisms: Group B reflects extreme lipid uptake and lipoprotein synthesis, Group C partial suppression of uptake pathways, and Group D a compensatory balance between lipid clearance and production. as shown in (Figure 1) and (Table 6).

Table 4: Biochemical Parameters of control and treated groups

Groups	Serum glucose mg/dl	Insulin pmol/dl	HOMA-IR
Control	112.12 ± 15.60 d	45.19 ± 4.58 a	1.8 ± 0.04 c
Dyslipidemia	131.64 ± 6.22 c	41.49 ± 3.34 b	1.94 ± 0.04 c
Diabetic and Dyslipidemia	290 ± 14.77 b	30.74 ± 3.97 c	3.14 ± 0.12 b
Diabetic	460 ± 12.21 a	31.80 ± 3.29 c	4.97 ± 0.23 a

Each value represents mean ± standard deviation (SD). Different letters within each column mean a significant difference between groups ($P \leq 0.05$).

Table 5: Lipid profile of control and treated groups

Groups	TC (mg/dl)	TG (mg/dl)	HDL (mg/ dl)	LDL (mg/dl)	VLDL (mg/ dl)
Control	55.64 ± 12.45 d	61.08 ± 11.85 d	51 ± 3.86 a	17.08 ± 2.53 c	12.22 ± 1.5 d
Dyslipidemia	80.55 ± 8.62 b	120.1 ± 11.88 b	41.67 ± 4.42 c	23.67 ± 3.56 b	24.02 ± 2.95 b
Diabetic and Dyslipidemia	110 ± 13.09 a	146 ± 18.74 a	48.2 ± 10.32 b	36 ± 10.21 a	29.4 ± 5.71 a
Diabetic	64.3 ± 11.59 c	74.6 ± 8.13 c	36.4 ± 5.15 d	14.5 ± 1.72 d	14.92 ± 1.52 c

Each value represents mean ± SD. Different letters within each column mean a significant difference between groups ($P \leq 0.05$).

Table 6: GAPDH, LPL, LDLR, APOB and APOE gene expression in all groups

Groups	Genes				
	GAPDH	LPL	LDLR	APOB	APOE
Control	1.12±0.2 c	1.09±0.10 c	1.17±0.12 c	1.24±0.15 d	1.48±0.12 d
Dyslipidemia	1.28±0.12 b	0.30±0.08 b	6.90±2.04 a	6.82±1.64 a	5.65±1.23 a
Diabetic and dyslipidemia	1.23±0.14 b	0.34±0.06 b	0.54±0.10 d	4.28±0.86 c	2.99±0.59 b
Diabetic	1.41±0.21a	1.75±0.3 a	2.27±0.78 b	4.92±1.24 b	2.60±0.41 c

Every value indicates mean ± SD. Distinct letters in each row denote a statistically significant difference ($P \leq 0.05$) relative to the control group.

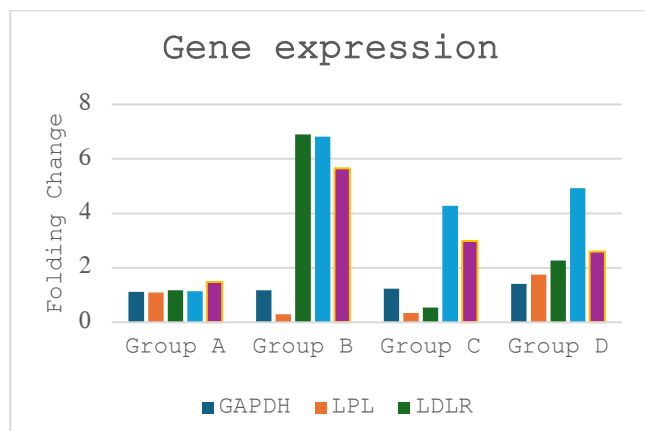


Figure 1: GAPDH, LPL, LDLR, APOB, and APOE gene expression in all groups.

Discussion

Diabetes and dyslipidemia were successfully induced in rats by relatively simple and low-cost methodology to create a model of analogue to human and pet animal, and this paved the road to more extended works in the future. However, an essential enzyme closely connected to triglyceride metabolism is lipoprotein lipase, which mainly hydrolyzes these fats inside circulating lipoproteins, mostly VLDL and chylomicrons (39,40). Triglyceride clearance and general lipid metabolism depend on LPL. Changes in the LPL gene expression can interfere with these mechanisms, hence causing dyslipidemia and higher cardiovascular risk (41). Several elements control LPL's activity: its expression levels, post-translational changes, and the presence of activators or inhibitors (42). The study done by Huang *et al* (43) demonstrates that the dyslipidemia group of rats downregulates LPL gene expression, that high-fat diets and obesity downregulate LPL expression in adipose tissue, hence causing hypertriglyceridemia (43). Peroxisome proliferator-activated receptor gamma (PPAR γ) is crucial in regulating glucose metabolism by facilitating glucose uptake into cells, particularly through the GLUT4 transporter. It also enhances insulin sensitivity in adipocytes, making it an important target in the pathophysiology and treatment of diabetes mellitus. Meanwhile, angiopoietin-like 4 (ANGPTL4) inhibits lipoprotein lipase (LPL), resulting in increased triglyceride levels, which may contribute to the dyslipidemia often associated with diabetes (43). The HFD + STZ rat model induces insulin resistance, hypertriglyceridemia, and hypercholesterolemia (44). Transcriptomic studies in this model show dysregulated lipid metabolism pathways, includes decreased expression of genes associated with lipid clearance (like LPL) (45). However, LPL gene expression in the diabetes group was upregulated. In contrast to type two diabetic rats, the LPL

gene was found to be upregulated in visceral adipose tissue. This upregulation is associated with the diabetic state, characterized by hyperglycemia, hyperlipidemia, and insulin resistance, which are more common in rats were given a HFD and received STZ (46). Previous studies agree with our results.

The LDLR gene's expression is controlled by many transcription factors and pathways for signaling. For instance, certain SNPs in the LDLR gene provide binding sites for transcription factors that promote gene expression, hence reducing LDL-C levels and lowering coronary heart disease risk (47). Non-sterol mediators also influence the post-transcriptional control of LDLR, hence changing its function and expression. Also, maintaining cholesterol balance and avoiding dyslipidemia depend on this control (48). Research in mice has revealed that the lack of LDLR, especially in hepatocytes, causes notable rises in plasma cholesterol levels under various diets, hence highlighting the vital function of LDLR in cholesterol homeostasis (49). A study agrees with our results done by Hussein and Mustafa on rats on a 5-week HFD with higher cholesterol (e.g., 3%) demonstrated a 7-fold rise in hepatic LDLR mRNA expression and higher LDLR protein levels (18.6 ng/ml vs. 3.45 ng/ml in controls) (20). Sterol regulatory element-binding proteins (SREBPs) stimulating LDLR transcription is probably what drives this increase as a compensatory reaction to hyperlipidemia. In contrast, a study done by Zeng *et al* (2016) on Sprague Dawley rats given an HFD for four weeks found a notable drop in hepatic LDLR mRNA expression, which corresponded with higher serum LDL-C and liver steatosis (50). Though notable rises in LDL-C and triglycerides, a different investigation on SD rats given a 3% cholesterol-enriched HFD for four weeks reported no meaningful alterations in hepatic LDLR mRNA expression relative to controls (51). Along with significant hepatic lipid buildup, hamsters on HFD exhibited significantly more LDLR mRNA suppression than rats (52). Despite consistent mRNA, rats on an HFD with regular caloric consumption showed higher LDLR protein levels (by lower degradation). Lower plasma PCSK9 helped to improve LDL clearance through this adaptation (53). Streptozotocin-induced diabetes significantly decreased elevated liver LDLR mRNA level along with an increasing in blood cholesterol levels (54). Conflicting findings might be explained by variations in rat strains, STZ dose, or project duration. Severe or protracted hyperglycemia, for instance, might lower hepatic LDLR transcription through oxidative stress or lower SREBP activity. In contrast to our results, a study about HFD/STZ-induced diabetic rats shows that hepatic LDLR mRNA expression fell with lower SREBP-2 activity (a major Transcriptional regulator of LDL receptor. Genes associated in the biosynthesis of cholesterol, such as HMGCoA reductase, were also downregulated, hence aggravating dyslipidemia (55).

APOB gene expression rises markedly in dyslipidemic rats on an HFD. Experimental results revealing a 12-fold rise in ApoB gene expression in dyslipidemic rats relative to controls, together with increased lipid metabolism pathways, support this conclusion (20). Rodent studies indicate that APOB overexpression is related to higher LDL cholesterol and atherogenic indices, hence stressing its involvement in dyslipidemia development (56). By encouraging its breakdown and blocking microsomal triglyceride transfer protein (MTP), insulin usually reduces APOB production (57). Rats on HFD as part of a metabolic syndrome model had higher APOB levels, as suggested by higher Apo B/Apo A1 ratios. A high-fat diet seems to worsen dyslipidemia by raising the synthesis of atherogenic lipoproteins, particularly those containing APOB (58). Although LDL receptor (LDLR) expression in HFD/STZ rats is lower (58), hepatic APOB overexpression continues as a compensatory reaction to fat accumulation, hence aggravating the synthesis of atherogenic lipoproteins (46,59). Insulin resistance and liver lipid overload in HFD+STZ animals (mimicking diabetic dyslipidemia) push APOB overexpression to control lipid export (46). STZ-diabetic rats' hepatic RNA Northern blot study revealed no difference in APOB mRNA levels as compared to controls (60).

A key component in lipid metabolism, the apolipoprotein E gene shows allelic variants that greatly affect a person's vulnerability to certain metabolic and neurological diseases. Housed on chromosome 19 (Human), the APOE gene shows a polymorphic structure defined by Three main alleles: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, which represent for three isoforms, namely apoE2, apoE3, and apoE4., all of which differ from one another by just one or two amino acids but display different functional characteristics (61,62). A study done by Srivastava shows that animals on cholesterol-rich diets have much higher apoE mRNA levels, suggesting a transcriptional control system. This implies that the transcription of the APOE gene is directly affected by dietary cholesterol, hence raising apoE production in the liver (62), which agree with our result. On the other hand, while plasma apoE levels could rise, meals high in saturated fats do not much change hepatic apoE mRNA levels. This suggests that post-transcriptional mechanisms, such as reduced receptor-mediated absorption of apoE-containing particles, may allow saturated fats to control apoE (62). ApoE mRNA Concentration in the liver remain constant in STZ-induced diabetic mice. despite generalized hyperglycemia and insulin shortage (63), previous study done by Wang *et al* (63) doesn't agree with our results.

Conclusion

Diabetes mellitus was successfully induced experimentally in adult male rats with STZ at the dose of 50 mg/kg. The experimental induction of dyslipidemia in adult

male rats using a HFD for 45 days was considered acceptable; moreover, dyslipidemia corresponds with the downregulation of the LPL gene and upregulation of LDLR, APOB, and APOE gene expression serves as a compensatory strategy to fight high lipid levels. While diabetes corresponded with a lower level of upregulation compared to dyslipidemia. Finally, the comorbidity of diabetes with dyslipidemia demonstrated a worsening synergistic impact on the considered parameters.

Acknowledgment

The authors are grateful to the College of Veterinary Medicine at the University of Mosul for providing non-financial assistance for this study.

Conflict of interest

None

References

1. Chaudhari YS, Bhujbal SS, Walunj VA, Bhor NS, Vyavhare RD. Diabetes mellitus: A review. *Int J Adv Res Sci Commun Technol*. 2023;16-22. DOI: [10.48175/ijarsct-8551](https://doi.org/10.48175/ijarsct-8551)
2. Mengstie MA, Seid MA, Gebeyehu NA, Adella GA, Kassie GA, Bayih WA, Gesese MM, Anley DT, Feleke SF, Zemene MA, Dessie AM. Ferroptosis in diabetic nephropathy: mechanisms and therapeutic implications. *Metab Open*. 2023;18:100243. DOI: [10.1016/j.metop.2023.100243](https://doi.org/10.1016/j.metop.2023.100243)
3. Jain N. Dyslipidemia: Risk factors, types and preventive measures. *Int J Sci Res*. 2023;12(6):1951–3. DOI: [10.21275/sr23617141631](https://doi.org/10.21275/sr23617141631)
4. Jialal I, Singh G. Management of diabetic dyslipidemia: an update. *World J Diabetes*. 2019;10(5):280-290. DOI: [10.4239/WJD.V10.I5.280](https://doi.org/10.4239/WJD.V10.I5.280)
5. Filippatos TD, Tsimihodimos V, Pappa E, Elisaf M. Pathophysiology of diabetic dyslipidaemia. *Curr Vasc Pharmacol*. 2017;15(6):566-575. DOI: [10.2174/1570161115666170201105425](https://doi.org/10.2174/1570161115666170201105425)
6. Kalra S, Raizada N. Dyslipidemia in diabetes. *Indian Heart J*. 2023. DOI: [10.1016/j.ihj.2023.11.002](https://doi.org/10.1016/j.ihj.2023.11.002)
7. Hirsu AM, Abdi AA, Peris A, Jacinto A, Muhammad P, Nur IA, Mohamud MH, Hussein M, Qaws A, Jayte M. Patterns and factors associated with dyslipidemia among patients with diabetes mellitus attending Hoima Regional Referral Hospital, Uganda. *Int J Gen Med*. 2025;18:73-86. DOI: [10.2147/ijgm.s494941](https://doi.org/10.2147/ijgm.s494941)
8. Osman E, Shawky H, Abbas RM, Metwaly A, Ibrahim A, Khanany FM. Association of LDLR gene polymorphism with the risk of cardiovascular disease in end-stage kidney disease patients on maintenance hemodialysis. *Indian J Nephrol*. 2024;35(1):29. DOI: [10.25259/ijn.33.2024](https://doi.org/10.25259/ijn.33.2024)
9. Jha CK, Mir R, Elfaki I, Banu S, Chahal SS. LDLR gene polymorphisms (rs5925 and rs1529729) are associated with susceptibility to coronary artery disease in a South Indian population. *Med Sci*. 2019;7(7):80. DOI: [10.3390/MEDSCI7070080](https://doi.org/10.3390/MEDSCI7070080)
10. Zhang Y, Ma KL, Ruan XZ, Liu BC. Dysregulation of the low-density lipoprotein receptor pathway is involved in lipid disorder-mediated organ injury. *Int J Biol Sci*. 2016;12(5):569-579. DOI: [10.7150/IJBS.14027](https://doi.org/10.7150/IJBS.14027)
11. Paalvast Y, De Boer JF, Groen AK. Developments in intestinal cholesterol transport and triglyceride absorption. *Curr Opin Lipidol*. 2017;28(3):248-254. DOI: [10.1097/mol.0000000000000415](https://doi.org/10.1097/mol.0000000000000415)

12. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, Francis GA, Genest J, Grégoire J, Grover SA, Gupta M. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. *Can J Cardiol.* 2021;37(8):1129-1150. DOI: [10.1016/J.cjca.2021.03.016](https://doi.org/10.1016/J.cjca.2021.03.016)
13. Gianazza E, Zoanni B, Mallia A, Brioschi M, Colombo GI, Banfi C. Proteomic studies on apoB-containing lipoprotein in cardiovascular research: A comprehensive review. *Mass Spectrom Rev.* 2023;42(4):1397-1423. DOI: [10.1002/mas.21747](https://doi.org/10.1002/mas.21747)
14. Yang CY, Gu ZW, Yang M, Gotto Jr AM. Primary structure of apoB-100. *Chem Phys Lipids.* 1994;67:99-104. DOI: [10.1016/0009-3084\(94\)90128-7](https://doi.org/10.1016/0009-3084(94)90128-7)
15. Mehta A, Shapiro MD. Apolipoproteins in vascular biology and atherosclerotic disease. *Nat Rev Cardiol.* 2022;19(3):168-179. DOI: [10.1038/s41569-021-00613-5](https://doi.org/10.1038/s41569-021-00613-5)
16. Wheless A, Gunn KH, Neher SB. Macromolecular interactions of lipoprotein lipase (LPL). *Subcell Biochem.* 2024;139:179. DOI: [10.1007/978-3-031-58843-3_8](https://doi.org/10.1007/978-3-031-58843-3_8)
17. Institute of Laboratory Animal Resources (US). Committee on Care and Use of Laboratory Animals. Guide for the Care and Use of Laboratory Animals. USA: National Institutes of Health; 1986. [\[available at\]](#)
18. Mustafa NG, Hasan MK. Biochemical investigation of an experimentally induced metabolic syndrome in rats. *Indian J Anim Res.* 2020;54(2):168-172. DOI: [10.18805/ijar.b-1028](https://doi.org/10.18805/ijar.b-1028)
19. Salih SS, Al-Khashab EM. Role of rosuvastatin in bone metabolism of ovariectomized adult rats. *Iraqi J Vet Sci.* 2023;37(1):267-273. DOI: [10.33899/ijvs.2022.133840.2309](https://doi.org/10.33899/ijvs.2022.133840.2309)
20. Hussein AA, Mustafa NG. Impact of a high-fat diet on dyslipidemia and gene expression of low density lipoprotein receptors in male rats. *Iraqi J Vet Sci.* 2024;38(1):133-138. DOI: [10.33899/ijvs.2023.140070.3017](https://doi.org/10.33899/ijvs.2023.140070.3017)
21. Sharma M, Chan HK, Lavilla Jr CA, Uy MM, Froemming GR, Okechukwu PN. Induction of a single dose of streptozotocin (50 mg) in rat model causes insulin resistance with type 2 diabetes mellitus. *Fundam Clin Pharmacol.* 2023;37(4):769-778. DOI: [10.1111/fcp.12892](https://doi.org/10.1111/fcp.12892)
22. Yalniz M, Pour PM. Toxicology of the endocrine pancreas. In: Pour PM, editor. *Toxicology of the Pancreas*. USA: CRC Press; 2005. 560-597 p. [\[available at\]](#)
23. Al Makhzoomi AK. Histological profiling of the extracellular matrix of streptozotocin-induced diabetic nephropathy in experimental mice and rats, an analytical study. *Iraqi J Vet Sci.* 2025;39(2):361-375. DOI: [10.33899/ijvs.2025.155481.4041](https://doi.org/10.33899/ijvs.2025.155481.4041)
24. Mahmood NM, Mahmud AM, Maulood IM. Protective effects of melatonin on AT1, ACE2, and Mas genes expression in induced diabetic aortic rats. *Iraqi J Vet Sci.* 2024;38(2):449-459. DOI: [10.33899/ijvs.2023.144712.3324](https://doi.org/10.33899/ijvs.2023.144712.3324)
25. Ghasemi A, Khalifi S, Jedi S. Streptozotocin-nicotinamide-induced rat model of type 2 diabetes. *Acta Physiol Hung.* 2014;101(4):408-420. DOI: [10.1556/aphysiol.101.2014.4.2](https://doi.org/10.1556/aphysiol.101.2014.4.2)
26. Nayak Y, Hillemane V, Daroji VK, Jayashree BS, Unnikrishnan MK. Antidiabetic activity of benzopyrone analogues in nicotinamide-streptozotocin induced type 2 diabetes in rats. *Sci World J.* 2014;2014(1):854267. DOI: [10.1155/2014/854267](https://doi.org/10.1155/2014/854267)
27. Furman BL. Streptozotocin-induced diabetic models in mice and rats. *Curr Protoc.* 2021;1(4). DOI: [10.1002/CPZ1.78](https://doi.org/10.1002/CPZ1.78)
28. Udomkasemsab A, Prangthip P. High fat diet for induced dyslipidemia and cardiac pathological alterations in Wistar rats compared to Sprague Dawley rats. *Clin Investig Arterioscler.* 2019;31(2):56-62. DOI: [10.1016/j.arteri.2018.09.004](https://doi.org/10.1016/j.arteri.2018.09.004)
29. Szudzik M, Hutsch T, Chabowski D, Zajdel M, Ufnal M. Normal caloric intake with high-fat diet induces metabolic dysfunction-associated steatotic liver disease and dyslipidemia without obesity in rats. *Dent Sci Rep.* 2024;14(1). DOI: [10.1038/s41598-024-74193-y](https://doi.org/10.1038/s41598-024-74193-y)
30. Greenfield EA. Sampling and preparation of mouse and rat serum. *Cold Spring Harb Protoc.* 2017;2017(11). DOI: [10.1101/PDB.PROT100271](https://doi.org/10.1101/PDB.PROT100271)
31. Singh M, Pandya R, Chandra S, Sharma S. Stability of clinical chemistry and hematological analytes in preserved plasma and blood obtained from Wistar rats. *Scand J Lab Anim Sci.* 2015;41:1-6. [\[available at\]](#)
32. Carlsson A, Hallgren IB, Johansson H, Sandler S. Concomitant enzyme-linked immunosorbent assay measurements of rat insulin, rat C-peptide, and rat proinsulin from rat pancreatic islets: Effects of prolonged exposure to different glucose concentrations. *Endocrinol.* 2010;151(10):5048-5052. DOI: [10.1210/EN.2010-0433](https://doi.org/10.1210/EN.2010-0433)
33. Minh HV, Tien HA, Sinh CT, Thang DC, Chen CH, Tay JC, Siddique S, Wang TD, Sogunuru GP, Chia YC, Kario K. Assessment of preferred methods to measure insulin resistance in Asian patients with hypertension. *J Clin Hypert.* 2021;23(3):529-37. DOI: [10.1111/jch.14155](https://doi.org/10.1111/jch.14155)
34. Leary ET, Carlson TH. Lipid analysis for important clinical conditions. In: *Encyclopedia of Analytical Chemistry*. USA: John Wiley & Sons Ltd; 2006. DOI: [10.1002/9780470027318.A0509M](https://doi.org/10.1002/9780470027318.A0509M)
35. Liu L, Aboud O, Jones RA, Mrak RE, Griffin WT, Barger SW. Apolipoprotein E expression is elevated by interleukin 1 and other interleukin 1-induced factors. *J Neuroinflammation.* 2011;8: 1-12. DOI: [10.1186/1742-2094-8-175](https://doi.org/10.1186/1742-2094-8-175)
36. Liang XF, Ogata HY, Oku H. Effect of dietary fatty acids on lipoprotein lipase gene expression in the liver and visceral adipose tissue of fed and starved red sea bream *Pagrus major*. *Comp Biochem Physiol A Mol Integr Physiol.* 2002;132(4):913-919. DOI: [10.1016/s1095-6433\(02\)00118-6](https://doi.org/10.1016/s1095-6433(02)00118-6)
37. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2- $\Delta\Delta CT$ method. *Methods.* 2001;25(4):402-408. DOI: [10.1006/meth.2001.1262](https://doi.org/10.1006/meth.2001.1262)
38. Stoker P, Tian G, Kim JY. Analysis of variance (ANOVA). In: Ewing R, Park K, editors. *Statistical Methods for Practice and Research*. USA: Routledge; 2020. 197-219 p. DOI: [10.4324/9780429325021-11](https://doi.org/10.4324/9780429325021-11)
39. Whitacre BE, Howles P, Street S, Morris J, Swertfeger D, Davidson WS. Apolipoprotein E content of VLDL limits LPL-mediated triglyceride hydrolysis. *J Lipid Res.* 2021;63(1):100157. DOI: [10.1016/j.jlr.2021.100157](https://doi.org/10.1016/j.jlr.2021.100157)
40. Ali MA, Mustafa NG. A comparative histopathological study of pancreas, intestine, and liver of experimentally induced diabetes in rats. *Iraqi J Vet Sci.* 2023;37(4):971-978. DOI: [10.33899/IJVS.2023.138343.2791](https://doi.org/10.33899/IJVS.2023.138343.2791)
41. Barg E. Polymorphisms of lipoprotein lipase gene and their participation in metabolic processes. *Pediatr Endocrinol Diabetes Metab.* 2011;17(2):107-112. [\[available at\]](#)
42. Sun W, Li P, Cai J, Ma J, Zhang X, Song Y, Liu Y. Lipid metabolism: Immune regulation and therapeutic perspectives in systemic lupus erythematosus. *Front Immunol.* 2022;13:860586. DOI: [10.3389/fimmu.2022.860586](https://doi.org/10.3389/fimmu.2022.860586)
43. Huang Y, Chen L, Li L, Qi Y, Tong H, Wu H, Xu J, Leng L, Cheema S, Sun G, Xia Z. Downregulation of adipose LPL by PAR2 contributes to the development of hypertriglyceridemia. *JCI Insight.* 2024;9(13):e173240. DOI: [10.1172/jci.insight.173240](https://doi.org/10.1172/jci.insight.173240)
44. Srinivasan K, Viswanad B, Asrat L, Kaul CL, Ramarao PJ. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: A model for type 2 diabetes and pharmacological screening. *Pharmacol Res.* 2005;52(4):313-320. DOI: [10.1016/j.phrs.2005.05.004](https://doi.org/10.1016/j.phrs.2005.05.004)
45. Guerra-Ávila PL, Guzmán TJ, Vargas-Guerrero B, Domínguez-Rosales JA, Cervantes-Garduño AB, Salazar-Montes AM, Sánchez-Orozco LV, Gurrola-Díaz CM. Comparative screening of the liver gene expression profiles from type 1 and type 2 diabetes rat models. *Int J Mol Sci.* 2024;25(8):4151. DOI: [10.3390/ijms25084151](https://doi.org/10.3390/ijms25084151)
46. Yang J, Li G, Zhang F, Liu Y, Zhang D, Zhou W, Xu G, Yang Y, Luo M. Identification of variations of gene expression of visceral adipose and renal tissue in type 2 diabetic rats using cDNA representational difference analysis. *Chinese Med J.* 2003;116(04):529-33. [\[available at\]](#)
47. Fairwozy RH, White J, Palmen J, Kalea AZ, Humphries SE. Identification of the functional variant(s) that explain the low-density lipoprotein receptor (LDLR) GWAS SNP rs6511720 association with

- lower LDL-C and risk of CHD. PLoS One. 2016;11(12):e0167676. DOI: [10.1371/journal.pone.0167676](https://doi.org/10.1371/journal.pone.0167676)
48. Kong WJ, Liu J, Jiang JD. Human low-density lipoprotein receptor gene and its regulation. J Mol Med. 2006;84(1):29-36. DOI: [10.1007/s00109-005-0717-6](https://doi.org/10.1007/s00109-005-0717-6)
49. Sotin T, Smati S, Dijk W, Ayer A, Arnaud L, Lorant V, Frey S, Croyal M, Cariou B, Le May C. Consequences of total, hepatocyte or intestinal LDL receptor deficiency on dyslipidemia and atherosclerosis progression in mice. Atherosclerosis. 2023;379:S4. DOI: [10.1016/j.atherosclerosis.2023.06.893](https://doi.org/10.1016/j.atherosclerosis.2023.06.893)
50. Zeng XZ, Sun DS, Yao NY, Chen YC, Cai DC, Huang XH, Huang DH, Gan HG, Zeng QZ, Zhao JZ, Huang LH. Impaired reverse cholesterol transport and hepatic steatosis contribute to pathogenesis of high fat diet-induced hyperlipidemia in murine models. Trop J Pharm Res. 2016;15(4):701-708. DOI: [10.4314/tjpr.v15i4.5](https://doi.org/10.4314/tjpr.v15i4.5)
51. Jia YJ, Liu J, Guo YL, Xu RX, Sun J, Li JJ. Dyslipidemia in rat fed with high-fat diet is not associated with PCSK9-LDL-receptor pathway but ageing. J Geriatr Cardiol. 2013;10(4):361-368. DOI: [10.3969/j.issn.1671-5411.2013.04.007](https://doi.org/10.3969/j.issn.1671-5411.2013.04.007)
52. Szudzik M, Hutsch T, Chabowski D, Zajdel M, Ufnal M. Normal caloric intake with high-fat diet induces metabolic dysfunction-associated steatotic liver disease and dyslipidemia without obesity in rats. Sci Rep. 2024;14(1):22796. DOI: [10.1038/s41598-024-74193-y](https://doi.org/10.1038/s41598-024-74193-y)
53. Niesen M, Bedi M, Lopez D. Diabetes alters LDL receptor and PCSK9 expression in rat liver. Arch Biochem Biophys. 2008;470(2):111-115. DOI: [10.1016/j.abb.2007.11.009](https://doi.org/10.1016/j.abb.2007.11.009)
54. Al-Hayali MA, Hussein AA, Mustafa NG. MicroRNAs as biomarkers in induced metabolic syndrome in rats. Iraqi J Vet Sci. 2024;38(3):599-605. DOI: [10.3389/IJVS.2024.146755.3466](https://doi.org/10.3389/IJVS.2024.146755.3466)
55. Morita SY. Metabolism and modification of apolipoprotein B-containing lipoproteins involved in dyslipidemia and atherosclerosis. Biol Pharm Bull. 2016;39(1):1-24. DOI: [10.1248/bpb.b15-00716](https://doi.org/10.1248/bpb.b15-00716)
56. Haas ME, Attie AD, Biddinger SB. The regulation of ApoB metabolism by insulin. Trends Endocrinol Metab. 2013;24(8):391-397. DOI: [10.1016/j.tem.2013.04.001](https://doi.org/10.1016/j.tem.2013.04.001)
57. Alnami A, Bima A, Alamoudi A, Eldakhakhny B, Sakr H, Elsamanoudy A. Modulation of dyslipidemia markers Apo B/Apo A and triglycerides/HDL-cholesterol ratios by low-carbohydrate high-fat diet in a rat model of metabolic syndrome. Nutrients. 2022;14(9):1903. DOI: [10.3390/nu14091903](https://doi.org/10.3390/nu14091903)
58. Hirano T. Pathophysiology of diabetic dyslipidemia. J Atheroscler Thromb. 2018;25(9):771-782. DOI: [10.5551/jat.RV17023](https://doi.org/10.5551/jat.RV17023)
59. Sparks JD, Zolfaghari R, Sparks CE, Smith HC, Fisher EA. Impaired hepatic apolipoprotein B and E translation in streptozotocin diabetic rats. J Clin Invest. 1992;89(5):1418-1430. DOI: [10.1172/JCI115731](https://doi.org/10.1172/JCI115731)
60. Nakamura T, Watanabe A, Fujino T, Hosono T, Michikawa M. Apolipoprotein E4 (1-272) fragment is associated with mitochondrial proteins and affects mitochondrial function in neuronal cells. Mol Neurodegener. 2009;4(1):35. DOI: [10.1186/1750-1326-4-35](https://doi.org/10.1186/1750-1326-4-35)
61. Zhao X, Sun Q, Cao YQ, Ran X, Cao Y. Association between apolipoprotein gene polymorphisms and hyperlipidemia: A meta-analysis. BMC Genom Data. 2021;22(1):35. DOI: [10.1186/s12863-021-00968-1](https://doi.org/10.1186/s12863-021-00968-1)
62. Srivastava AK. Regulation of the apolipoprotein E by dietary lipids occurs by transcriptional and post-transcriptional mechanisms. Mol Cell Biochem. 1996;155(2):153-162. DOI: [10.1007/BF00229312](https://doi.org/10.1007/BF00229312)
63. Wang XT, Li J, Liu L, Hu N, Jin S, Liu C, Mei D, Liu XD. Tissue cholesterol content alterations in streptozotocin-induced diabetic rats. Acta Pharmacol Sin. 2012;33(6):909-917. DOI: [10.1038/aps.2012.50](https://doi.org/10.1038/aps.2012.50)

التعبير الجيني لـ LDLR, APOB, APOE, LPL في الجرذان التي تعاني من داء السكري واعتلال الشحوم التجريبي

هاريكار صالح محمود^١ و نشأت غالب مصطفى^٢

^١ طالب ماجستير، كيمياء حيائية بيطرية، فرع الفلسجة والكيمياء الحياتية والأدوية، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

يعد داء السكري من الامراض الايضية الشائعة في الانسان والحيوان وخاصة في الكلاب والقطط، ويرافق هذا الداء عادةً مجموعة من الاضطرابات الايضية للكاربوهيدرات والشحوم والبروتينات. تم اجراء هذه الدراسة للتعرف على الارتباط بين داء السكري واضطراب الشحوم المستحدثان تجريبيًا في الجرذان فيما يخص التعبير الجيني للجينات LDLR, APOB, APOE, LPL. استخدم ٦٤ من ذكور الجرذان المختبرية البيضاء البالغة في هذه الدراسة، اذ وزعت الى اربع مجاميع: المجموعة الاولى أعطيت الغذاء القياسي للجرذان (مجموعة السيطرة)، المجموعة الثانية أعطيت الغذاء عالي الشحوم HFD (مجموعة اضطراب الشحوم)، والمجموعة الثالثة أعطيت الغذاء عالي الشحوم HFD وحقت بالستربتوزونوسين STZ (٥٠ ملغم/كغم) (مجموعة اضطراب الشحوم وداء السكري)، والمجموعة الرابعة حقنت بالستربتوزونوسين STZ (٥٠ ملغم/كغم) واعطيت الغذاء القياسي (مجموعة داء السكري). أظهرت النتائج ان داء السكري واضطراب الشحوم تسبب بتغييرات معنوية في دلائل الشحوم ومقاومة الانسولين وقيم وزن الجسم، اذ لوحظ ان اضطراب الشحوم تسبب في ارتفاع معنوي في مستوى الكوليستيرول والشحوم الثلاثية، بينما تسبب الستربتوزونوسين في ارتفاع ملحوظ في نسبة سكر الدم مع انخفاض في مستوى الانسولين. كل هذا تسبب في تغييرات في التعبير الجيني للجينات قيد الدراسة (LDLR, APOB, APOE, LPL)، اذ لوحظ انخفاض في التعبير الجيني لجين LPL في مجاميع الدراسة عدا مجموعة داء السكري، بينما زاد التعبير الجيني لجين LDLR في مجموعة اضطراب الشحوم. يمكن الاستنتاج بان وجود اضطراب الشحوم مع داء السكري يزيد من تدهور القيم الكيموحيوية والتعبير الجيني اكثر من تأثير كل مرض لوحده.