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Impact of a high-fat diet on dyslipidemia and gene expression of low-density lipoprotein receptors in male rats

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Abstract

Dyslipidemia is one of the leading causes of heart disease in human and pet animals. This study aimed to induce experimental dyslipidemia in adult male rats by a simple method via a high-fat diet. The 30 adult male rats were grouped as follows: The first group (G1) was feds a standard diet orally for five weeks as a control, while the second group (G2) was given a high-fat diet (dyslipidemia group) for five weeks. Serum lipid profile confirmed the induction, in which there were elevated cholesterol, triacylglycerol, very low-density lipoproteins, low-density lipoproteins, and depressed high-density lipoprotein, so, the atherogenic index in the dyslipidemic group was more significant than the control rat group. Low-density lipoprotein receptor plays an essential role in the metabolism of lipids in the blood. Thus, there was an upregulation (about seven folds) in the expression of genes of the receptor of low-density lipoprotein corresponding with the elevated receptor protein concentration (18.6 ng/ml) when compared with the control group (1.91 ng/ml). It could be concluded that experimental dyslipidemia could be induced in adult rats by consuming a high-fat diet within five weeks, and it is related to gene expression upregulation and protein elevation of a receptor of low-density lipoprotein, and this may be a compensatory mechanism to challenge hyperlipidemia.

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Introduction

Dyslipidemia (usually called hyperlipidemia) is one of the most frequently recognized chronic diseases in humans and pet animals. It is characterized by elevated levels of triglycerides, serum cholesterol, or both, in addition to the abnormal levels of the associated lipoproteins (1). The most common and severe clinical concern of dyslipidemia is the atherosclerosis risk and related diseases of the cardiovascular system, that usually associated with classical upraises of total cholesterol (TC), triacylglycerol, and low-density lipoprotein (LDL), and suppressed high-density lipoprotein (HDL), also associated with an increase in lipoproteins (a) (Lpa) (2). On the other hand, dyslipidemias are a growing research area, with modern studies to provide awareness of their molecular foundation with genetic backgrounds (3). Both cholesterol and triacylglycerol are circulating inside the hydrophobic part of lipoprotein units, isolated and protected from aqueous blood plasma through outward apolipoproteins and phospholipids. Lipoprotein as a plasma protein has many classes; chylomicrons (CM), very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), and HDL; these classes are recognized by their size, density, function, lipid and protein content, and their crucial apolipoprotein. Interestingly, apolipoproteins are responsible for the constancy of the particles and work as a ligand for their specific receptors and as a cofactor for handling and carrier molecules (4,5). It is well-known that plasma triacylglycerol develops from nutritional sources and hepatic creation. Fatty acids of the diet are engaged by fatty acid transporters of intestinal enterocytes and are generated into triacylglycerol in a consequence manner (6,7). Intestinal intracellular SAR1B GTPase seems essential for gathering particles of CM (8),

whereas hepatic apo B-100 and apo B-48 are selective to chylomicrons and VLDL, respectively (3,9). Additional triacylglycerol reduction and CE improvement via hepatic lipase will produce LDL, eventually unoccupied through specific receptor LDL (LDLR) in the liver. These receptors are constantly salvaged until they are directed for deprivation through a definite convertase called PCSK9 (10,11). Whereas CEs are fragmented into free cholesterol via the acid lipase of liposomes. HDL is attributed to the converse carried of cholesterol from peripheral tissue to the liver. HDLs are consumed by liver scavenger receptor class B type 1 (SR-B1), and their cholesterol concentrates in the direction of bile excretion (12-14). On the other hand, LDLR is the cell surface receptor composed of 839 amino acids, and its vital function is cholesterol-rich LDL endocytosis (15-17). Interestingly, identifying ApoB100 is implanted in the phospholipid layer of VLDL. LDLR also recognizes ApoE, which exists in chylomicrons and IDL (18). For their identification of LDLR, Goldstein received Nobel Prize in Medicine or Physiology in 1985 (19). In addition, because the LDL receptor establishes the cholesterol-rich LDL endocytosis, it keeps the plasma LDL level. However, that ensues in each mammalian cell is chiefly in hepatic tissue eliminating about two-thirds of LDL from circulation (20).

Furthermore, more studies should be done to uncover the details of dyslipidemia and its related molecular origin by experimental induction and investigation in laboratory animals, which is the aim of this study.

Materials and methods

Study approval

This study was approved by an ethics committee that has been attained from the institutional animal care and committee of Veterinary Medicine at the College / University of Mosul, Iraq, with certified No. UM.VET.2018.02.

Experimental animals

All experimental works have been performed according to the guideline for the caring and use of laboratory animals of the National Institute of Health (21) and accepted by the lab animal care committee of the College of Veterinary Medicine, University of Mosul. Thirty male rats at three months and weighing in at 180-200 g were employed in this study. These rats were maintained below suitable conditions of environmental temperature (22±2ºC), well humidity, and dark/light cycle (12/12 hours) (22,23). Animals were grouped into the control group (CG) feds standard diet and the dyslipidemic group (DG). Rats were left for one week before the experiments to acclimatize. Furthermore, a standard pelleted diet fed to the control group (15 rats), comprises 60% carbohydrates, 26% crude protein, 5% lipids, 5% crude fiber, 2% vitamin premix, and 2% mineral premix (24). At the same time, dyslipidemia in 15 rats was induced by the high-fat diet (HFD) (1.5% cholesterol, 3% olive oil, and 0.5% cholic acid) for five weeks. Moreover, the diet and tap water were *ad libitum* (25). At the end of experiments (week 5), and after 12 hours of fasting, blood samples were taken from the retro-ocular vein of the eye, and the serum was separated; after that, rats were sacrificed, and the liver was taken out for further analysis.

Biochemical analysis

The collected blood was centrifuged for 15 minutes at 3000xg to separate the serum. Biochemical analysis of lipid profile includes; TC, TG, VLDL, LDL, and HDL, were estimated through automatic enzyme method (Genri-GS200-China), and atherogenic index (AI) is calculated as: AI = total cholesterol - HDL / HDL (26-28).

LDLR protein

Rat LDLR ELISA kit (double antibody sandwich technique), Cat No. MBS260387 (MyBiosource, USA) was utilized for the detection of LDLR protein (29), in brief; liver tissue slices and then washed out in phosphate buffer saline (PBS), add extraction of tissue protein reagent was and used ice water for mixing. After that, the mixture was centrifuged (3000xg at 4ºC) for 10 min, and the supernatant was tested immediately after many times washing and a specific reagent added according to the guideline of the manufacturer's instruction, by ELISA microplate reader (Biotek, USA) at a wavelength of 450nm. The LDLR protein concentration (ng/ml) is estimated by applying the standard curve.

mRNA isolation and RT-PCR

Isolation of mRNA from the liver as follows, about 10 mg liver sample was ground in a powder in the liquid nitrogen by pre-chilled pestle and mortar, immediately mixed with TRIzol (Ambion, Life Technologies, USA), lysis buffer delivered with the kit and the mRNA extracted by using Hybrid-RTM kit (GeneAll, Korea), steps have proceeded following the instructions of the manufacturer (30). Nanodrop 2000 (Thermo - Fisher Scientific, USA) (Thermo-Fisher Scientific, USA) was applied to measure the concentration of mRNA, and cDNA was ready with GoScript RNA invert transcriptase kit (Roche, China) based on the manufacturer's instructions. Gene expression was assessed using validated cDNA-specific primers (Table 1) in the quantitative real-time polymerase chain reaction (RT-PCR) by using SYBR green master mix (Roche, China), with Bio-Rad real-time PCR system (China) and the standard protocol of RT-PCR was done (Table 2). GAPDH primers that reflect an internal control (housekeeping gene) and Ct values of RT-PCR results were expressed as ΔΔ Ct and corrected for 2-ΔΔ Ct according to Livak's method (31) and represented as folds of increase or decrease of gene expression.

Table 1: primers of LDLR and GAPDH genes

Gene	Primers
LDLR	F 5'-ATTTTGGAGGATGAGAAGCAG-3'
	R 5'-CAGGGCGGGGAGGTGTGAGAA-3'
ApoB	F 5'-GAAAGCATGCTGAAAACAACC-3'
	R 5'-AGGCCTGACTCGTGGAAGAA-3'
GAPDH	F 5'-GCCATCAACGACCCCTTCATT-3'
	R 5'-CGCCTGCTTCACCACCTTCTT-3'

Table 2: Program of RT-PCR

Cycles		Temperature	Time
First cycle	Denaturation	94°C	3 min
	Annealing	60°C	1 min
	Extension	72°C	2 min
Subsequent 25 cycles	Denaturation	94°C	1 min
	Annealing	60°C	1 min
	Extension	72°C	2 min
Terminal	Extension	72°C	10 min

Statistical analysis

Result data are set as means ± SE using SPSS (ver. 22). The significance of differences between groups was assessed via one-way analysis of variance (ANOVA) with Duncan's test. A significant difference was considered at P≤0.05 (32).

Results

Dyslipidemia was successfully induced in rats by HFD within five weeks (Table 3). There is a significant elevation of TCs, triacylglycerol, VLDL, and LDL, and depression of HDL, so the atherogenic index (AI) in DG was more remarkable than normal rats (CG) about seven folds (Table 3). On the other hand, mRNA was isolated, and its purity was evaluated and confirmed by Nanodrop spectrophotometer. After the conversion of mRNA to cDNA, the latter was amplified by RT-PCR, and the LDLR gene and ApoB gene expression were determined as folds of changes according to the housekeeping GAPDH gene. There was a more significant elevation in LDLR gene expression of DG (Table 4) when compared to CG and depending on the GAPDH gene expression. Correspondingly, LDLR protein concentration (Figure 1) was significantly greater in DG when compared with CG. As well as, ApoB gene expression of DG rats were 12-fold greater when compared to CG and depending on the GAPDH.

Table 3: Lipid profile of control and dyslipidemic groups

Lipid profiles	Control	Dyslipidemic
Total cholesterol	94±3.2c	197±5.1a
Triacylglycerol	76±3.9c	142±4.0a
VLDL	14±0.6b	31±1.1a
LDL	32±1.2d	123±7.4a
HDL	45±3.8a	22±2.1c
AI	1.08±0.21e	7.95±0.94a

Each value represents mean (mg/dl)±S.E. Different letters in each row characterize a significant (P ≤ 0.05) difference compared to the control group.

Table 4: LDLR gene expression and protein concentration in DG and CG

Groups	GAPDH expression	LDLR expression	ApoB expression	LDLR (ng/ml)
Control	1.07±0.2a	1.13±0.1e	1.24±0.2e	3.45±1.0e
Dyslipidemic	1.91±0.3a	7.88±1.2a	15.71±2.2a	18.60±2.4a

Each value represents mean±S.E. Different letters in each row characterize a significant (P ≤ 0.05) difference compared to the control group.

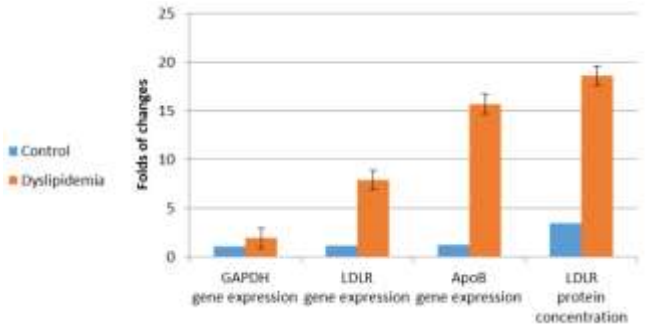

Figure 1: LDLR gene expression and protein concentration in DG and CG.

Discussion

Development of experimentally induced dyslipidemia in laboratory animals, particularly in rats, either via transgenic animals or by HFD, is applied extensively as a foundation for detailed recognition of the significant events in the pathophysiology of dyslipidemia. Whereas ApoB and LDLR genes seem to play a crucial turn in the initiation and development of dyslipidemia (33); thus, more comprehensive studies should be considered in this field .

However, a significant elevation of lipid profile confirmed the induction of experimental dyslipidemia successfully in rats in our work. These results agree with other authors (34-36), who documented that induced

dyslipidemia is characterized by a predominant elevation of lipid profiles (with depression of HDL). This may be because HFD contributed to the significant enhancement of liver cholesterol and triacylglycerol, Also, the concentration of hepatic triacylglycerol is controlled by beta-oxidation, triacylglycerol synthesis, and liberation from lipoproteins. As well as, HFD may reduce fatty acid catabolism which enhances the hepatic synthesis of triacylglycerol (37,38). Dyslipidemia comprises the disproportion of cholesterol levels (39). Elevated body TC is one of the crucial causes of dyslipidemia. Cholesterol homeostasis depends on the absorption, synthesis, and excretion pathways (40). About two- thirds of the body's cholesterol is formed by the liver, the main organ for endogenous cholesterol synthesis. The cholesterol synthesis pathway is a complicated procedure (about 25 enzymatic reactions are required), but the essential feature is two key necessary rate-limiting enzymes, hydroxyl-methyl-glutaryl - CoA reductase (HMGCR) and synthase (HMGCS) (41).

Consistently, in the developmental stage of atherosclerosis, vascular endothelial damage (due to the multifactorial etiology such as hyperlipidemia, hypertension, DM, smoking, and other harmful inducers), the increased intimal permeability, then a few LDL particles infiltrate the vascular endothelium, and has become immobile in the arterial membrane, these particles of LDL are oxidized into a form the hazardous oxidized LDL (ox-LDL). The latter uptake through macrophages forms foam cells which always aggregate and then combine to form lipid central (atherosclerotic plaque). In comparison, HDL reverses the transport of cholesterol from the peripheral sites to the liver, and can diminish Ox-LDL, cutting the pathogenesis course and preventing the development of atherosclerosis (42). Thus, the atherogenic index (AI), symbolizing serum total cholesterol and HDL, reveals a dominant figure in cardiometabolic health and atherogenicity, so it is considered a novel biomarker in clinical medicine (43). The outcome of this study exposes that the HFD, which leads to hyperlipidemia, will be contributed to a prominent elevation of AI.

Though, LDLR accomplishes cholesterol homeostasis, LDL binds its receptors (LDLR) on liver cell membranes, and by endocytosis, the complexes enter the hepatocyte. Interestingly, LDL is released (at the acidic pH of the endosome), allowing LDLR recycling to the cell membrane (44). LDLR is located on chromosome 8q13 and is a family of transmembrane receptors contributing to a diversity of critical biological functions associated with endocytosis and signal transduction pathways. LDLR as a protein consists of 839 amino acid residues (in humans) that are assembled in five domains: ligand binding, cytoplasmatic, glycosylated, EGF precursor homologous, and transmembrane. The ligand binding domain is responsible for lipoprotein binding (45,46). As mentioned above, LDLR contributes mainly to the elimination of LDL from the circulation; thus, when there is a defect in this receptor (as in the familiar hypercholesterolemia (FH) in humans) (47). Consequently, there is an elevation of the blood lipid profile Correspondingly a higher lipid profile will encourage the LDLR expression gene (so LDLR protein) to overcome hyperlipidemia; this result agrees with other authors (45-47).

Conclusion

Successfully dyslipidemia is developed experimentally by a simplified approach in adult male rats through HFD within five weeks, and dyslipidemia corresponds with upregulation of LDLR gene and protein as a compensatory mechanism to fight elevated lipid profiles.

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Conflicts of Interest

The authors declare that they have no competing interests.

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تأثير النظام الغذائي الغني بالدهون على اضطراب شحميات الدم والتعبير الجيني لمستقبلات البروتين الدهني منخفضة الكثافة في ذكور الجرذان

احمد علي حسين و نشأت غالب مصطفى

فرع الفسلجة والكيمياء الحياتية والأدوية، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

اضطراب شحميات الدم هو أحد الأسباب الرئيسية لأمراض القلب لدى الإنسان والحيوانات الأليفة. الهدف من هذه الدراسة هو استحداث اضطراب شحميات الدم التجريبي في ذكور الجرذان البالغة بطريقة بسيطة عن طريق نظام غذائي عالي الدهون. تم اخذ ٣٠ ذكر من الجرذان البالغة على النحو التالي: أعطيت المجموعة الأولى محلول نظام غذائي قياسي عن طريق الفم لمدة ٥ أسابيع واعتبر مجموعة سيطرة، بينما أعطيت المجموعة الثانية نظام غذائي عالي الدهون (مجموعة اضطراب شحميات الدم) ولمدة ٥ أسابيع. فحص الدهنيات في المصل يؤكد هذا الاستحداث، حيث كان هناك ارتفاع في نسبة الكوليسترول، الدهون الثلاثية، البروتينات الدهنية منخفضة الكثافة ومنخفضة الكثافة جدا وخفض البروتينات الدهنية عالية الكثافة، لذلك كان مؤشر تصلب الشرايين في مجموعة اضطراب شحميات الدم أكبر من مجموعة السيطرة. تلعب مستقبلات البروتين الدهني منخفض الكثافة دورا رئيسيا في أيض الدهون بالدم، بالتالي، كان هناك تنظيم زيادة في التعبير الجيني لمستقبل البروتين الدهني منخفض الكثافة والمقابل لارتفاع تركيز مستقبلات البروتين. يمكن أن نستنتج أن اضطراب شحميات الدم التجريبي يمكن أن يحدث في الجرذان البالغة من خلال اتباع نظام غذائي عالي الدهون في غضون خمسة أسابيع، وهو مرتبط بزيادة تنظيم التعبير الجيني وارتفاع البروتين لمستقبلات البروتين الدهني منخفض الكثافة، وقد تكون هذه آلية تعويضية لتحدي فرط شحميات الدم.