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THE EFFECTS OF ENDURANCE TRAINING AND ESTROGEN-RELATED RECEPTOR α DISRUPTION ON MITOFUSIN 1 AND 2, GLUT2, PPARβ/δ AND SCD1 EXPRESSION IN THE LIVER OF DIABETIC RATS

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Diabetes is a progressive and metabolic disease with a high prevalence throughout the world. Physical activity is considered as an intervention to improve diabetes. Intervention such as estrogen-related receptor α (ERRα) inhibition is considered as a new way to manage diabetes. In current study, we examined ERRα inhibition along with exercise training (ET) on the gene expression of mitofusin 1 (MFN1), MFN2, glucose transporter 2 (GLUT2), peroxisome proliferator-activated receptor beta or delta (PPARβ/δ), and stearoyl-CoA desaturase 1 (SCD1) in rat liver. The animals were divided into 8 groups (n = 7); 1, Control (CTL) 2, Diabetes (D) 3, ERRα inhibition (ERRI) 4, Endurance Training (ET) 5, Diabetes+ERRα inhibition (D+ERRI) 6, Diabetes+Endurance training (D+ET) 7, Endurance Training+ERRα inhibition (ET+ERRI) 8, Diabetes+Endurance Training+ERRα inhibition (D+ET+ERRI). The liver tissues were used for Real-Time PCR. The results showed that ET significantly increased PPARδ, MFN1 and, MFN2 expression in control rats compared to D group. In ERRI group, SCD1, GLUT2, MFN1 and MFN2 gene expression was increased compared to CTL and DM group. In CTL and D rats, the combination of ERRα inhibition and ET significantly and additively increased MFN1, MFN2, and GLUT2 expression. Overall, the combination of ET and ERRα inhibition probably can be considered as a potential therapeutic intervention for treatment of metabolic diseases including diabetes and cardiovascular disease.

K e y w o r d s: diabetes, estrogen related receptor alpha (ERRα), GLUT2, mitofusin, PPARβ/δ, SCD1.

Despite available medications and managements, diabetes is still a widespread metabolic disease characterized by insulin secretion and function defects and hyperglycemia. Diabetes prevalence is increasing and estimated to affects about 5.4% of the world population by 2025. Therefore, promising and valuable management is needed to reduce diabetes and its complications. The attention on exercise and physical activity to reduce diabetes complications was increased [1].

Endurance training (ET) described as an aerobic training that is a good alternative for diabetic patients. ET showed beneficial effects on diabetes such as reduced hyperglycemia, improved lipid profile, decrease body weight, and increase insulin sensitivity and mitochondrial size and contents [2-4]. Therefore, much attention has been paid to the beneficial effects of exercise on the prevention and treatment of diabetes [5, 6].

The dynamic of mitochondria is maintained by a balance between fusion and division [7]. Disturbed mitochondrial dynamic and function are related to diabetes and insulin resistance pathogenesis [4]. It has been described that Mitofusin (MFN) proteins modulates mitochondria dynamic and biogenesis. MFN1 and MFN2 were up-regulated by exercise training, and this elevation was mediated by Peroxisome proliferator-activated receptor gamma coactivator 1-α/Estrogen-related receptor α (PGC-1α/ERRα). Also, it has been shown that MFN2 inactivation results in mitochondrial dysfunction and defect in mitochondrial fusion that reduces mitochondrial oxidative capacity [4].

The estrogen-related receptors (ERRs) are important for regulation of cellular energy metabolism [8, 9]. ERRα expressed in a tissue specific manner and expressed in tissues with high oxidative metabolism demands such as skeletal muscle, adipose tissue, and liver where it affects carbohydrate and lipid metabolism, and mitochondrial activity. ERRα inhibition is related to reduce body weight and ERRα$^{-/-}$ mice showed reduced serum glucose and improved insulin sensitivity [9].

Unlike adipose tissue and skeletal muscles, the transport of glucose into hepatocytes is not a rate-limiting step. In fact, transport of glucose into the adipose tissue and skeletal muscles is an insulin-dependent process, but in hepatocytes, this transportation is not insulin-dependent. This transportation process conducted through the membrane facilitated-diffusion glucose transporters family that their distribution is tissue-specific. Glucose transporter 2 (GLUT2) is mainly expressed in the liver and on the other hand, GLUT4 is mainly expressed in adipose tissue and skeletal muscle [10]. The expression of GLUT2 in the liver is reduced by insulin and increased by glucose level. Also, it was reported that GLUT2 is acting as a glucose sensor in the liver [11]. The data reported over the GLUT2 expression in the liver of diabetic models are controversial [10-16]. It has been described that GLUT2 expression was increased in diabetic rats and this elevation was reduced to normal by insulin therapy [10]. Also, GLUT2 gene and protein expression decreased in diabetic mice and rats, and this reduction was related to glucose-stimulated insulin secretion [11, 12]. Rathinam and Pari (2016) reported that liver GLUT2 expression was reduced in STZ-induced diabetic rats [13]. Sandoval-Muníz et al have found that gene expression of GLUT2 was increased after diabetes induction by STZ compared to control group [14]. Also, Jurysta et al showed that GLUT2 expression was up-regulated in the liver and lung [16].

Mitochondria have a vital role in energy metabolism and its defects are connected to liver dysfunction. There are proteins that involved in the mitochondrial dynamic network including MFN1, MFN2, optic atrophy 1 (OPA1) and dynamin-related protein (DRP1) [17]. Mitochondrial dynamic is dependent on the balance between fusion or fission and precise functioning of mitochondrial biogenesis. It was suggested that the possible imbalance in those processes is connected to metabolic disease [18]. MFN1 and MFN2 showed high similarity (about 60%) and are involved in mitochondrial fusion. But it was revealed that MFN2 has other functions, for example, the connection between MFN2 and cellular metabolism was described in diabetes [18, 19]. Reduced rat liver MFN2 activity was related to the metabolic disorders such as diabetes, decreased glucose oxidation, and tricarboxylic acid (TCA) cycle activity [18]. Also, it was confirmed by Soriano and colleague (2006) that MFN2 expression in diabetes was reduced [19]. It has been reported that ERRα up-regulated MFN2 gene expression. This was documented that improved insulin sensitivity after exercise was related to MFN2 up-regulation [19]. PGC-1α/ERRα exerts their role in mitochondrial fusion thorough MFN2 elevation [4]. Exercise is considered as an important factor that decreased mitochondrial imbalance [20]. Koo and Kong found that exercise on treadmill increased fusion proteins such as OPA1, MFN1 and MFN2 in the brain [20].

PPARs are transcriptional factors belong to the nuclear hormone receptor superfamily. There are three isotypes of PPAR family designated as PPARα, PPARβ/δ, and PPARγ [21]. They control various gene expression involved in carbohydrate/lipid metabolism, cell differentiation and proliferation. PPARδ regulates cellular energy homeostasis and involved in Fatty acid oxidation (FAO), mitochondrial oxidative phosphorylation and FA transport [21, 22]. PPARδ affects liver and peripheral tissue energy consumption and therefore attenuates insulin resistance. PPARδ increases insulin secretion and glucose homeostasis, and influenced FAO. These PPARδ functions proved its protective effects against insulin resistance, obesity, hepatosteatosis, diabetes and atherosclerosis [22, 23]. Cheng et al have reported that exercise beneficial effects on vascular functions mediated thorough PPARδ [24]. Changes

in substrate consumption from carbohydrates toward lipids are a marker of training. Fan and colleagues (2017) showed that PPARδ is related to ET in mice and PPARδ up-regulation significantly reduced glucose oxidation [25].

Stearoyl CoA Desaturase 1 (SCD1) is involved in monounsaturated FAs synthesis that controls this process. SCD1 is also important for TG production and storage. SCD activity increased in diabetes and is correlated with obesity and cardiovascular disease (CVD) [26]. Shen et al reported that SCD1 expression was increased after high far diet but not by exercise training [27]. Yasari and coworkers (2010) reported that 8-week exercise program remarkably down-regulated hepatic SCD1 protein and gene expression [28]. A single bout of ET raised SCD index [29]. It has been documented that SCD1 is necessary for triggering diet-induced insulin resistance at the liver level [30, 31].

ERRα regulates energy metabolism and affects fuel expenditure. Beneficial effects of ET on metabolism in diabetes were confirmed. In this study, we examined the expression of genes involved in mitochondrial fusion (MFN1 and MFN2), and GLUT2 that sensing glucose in the liver, and other genes that regulate lipid metabolism (PPARδ and SCD1 expression) in the liver of non-diabetic and diabetic rats that performed ET. ERRα was inhibited and a combination of both (ET+ERRα inhibition) to evaluate ERRα inhibition effects on genes involved in metabolism and mitochondrial dynamic in diabetic models along with ET.

Materials and Methods:

Materials. XCT790 (Sigma, X4753), STZ (Sigma, No: S0130), Total RNA isolation kit (Bio Basic; BS414), cDNA synthesis kit (TAKARA; RR037A), SYBR Green (Ampliqon; A325402).

Study groups. All the animal procedures were in accordance with the requirements of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes. This study was approved by the ethics committee of the Kerman Medical University Research Council (No. IR.KMU.REC13970321). In this study, we used 56 male Wistar rats in 8 groups (weight, 190 ± 15 g). The animals were maintained at controlled condition, 24 ± 2°C, 12/12 h light/dark cycle, and free access to chow diet and water. After acclimatization with new condition, the animals were randomly divided into 8 groups that were as follows; 1, Control (CTL) 2, Diabetes Mellitus (DM; STZ-induced diabetic that received an i.p. dose of STZ (45 mg/kg)) 3, ERRα inhibition (ERRI; received daily i.p. injection of 0.48 mg/kg of XCT790) 4, Endurance Training (ET) 5, Diabetes Mellitus+ERRα inhibition (DM+ERRI) 6, Diabetes Mellitus+Endurance training (DM+ET) 7, ERR inhibition+Enduranc Training (ERRI+ET) 8, Diabetes Mellitus+Endurance Training+ERRα inhibition (DM+ET+ERRI). The duration of the study was 4 weeks and at the end of the study, animals were sacrificed and abdominal part was incised and liver was dissected and washed with cold saline and finally freeze by liquid nitrogen. The obtained liver tissues were stored at -80 until future measurements [32].

Diabetes induction. The experimental diabetes was induced before ET and by a single dose of i.p. injection of STZ (45 mg/kg prepared in 0.1 M citrate buffer, pH 4.5) in rats that were fasted overnight. Three days after STZ injection fasting blood glucose (FBG) in overnight fasted animals was measured by glucometer (Accu-Check, Germany) to confirm diabetes induction. Animals with FBG higher than 250 mg/dl were confirmed as diabetic models and randomly entered into diabetic groups of the study.

Endurance training (ET) protocol. Animals performed ET for 4 weeks (5 days per week). The groups that have to carry out training were familiarized with training protocol on a treadmill at low-speed (15-20 m/min) for a week. Then, the duration was gradually raised for 4 weeks. In the last two weeks, rats trained 50 min daily (27 m/min) (13 p.m for about 5 h) [33].

ERRα inhibition. This was indicated that ERRα can be inhibited by the thiadiazole acrylamide (XCT790-$C_{23}H_{13}F_9N_4O_3S$). Therefore, in this study we inhibited ERRα by daily XCT790 (0.48 mg/kg) intraperitoneal injections for 28 days (Diagram) (7:30 a.m for about 30 min) [8, 32].

Total RNA extraction, cDNA synthesis and Real-time PCR. We used 50 mg of the liver for total RNA extraction. The liver tissue was homogenized at lysis buffer by Sonicator (Heilscher H200, Germany), total RNA was extracted by the EZ-10 Spin Column according to Bio Basic kit's protocol. Next, the cDNA was synthesized from extracted total RNA (600 ng) by TAKARA cDNA synthesis kit. We used gene-specific primers for Real-time PCR which purchased from metabion international (metabion GmbH, Germany) (Table). Each Real-time PCR reaction contained 10 µl Ampliqon SYBR green,

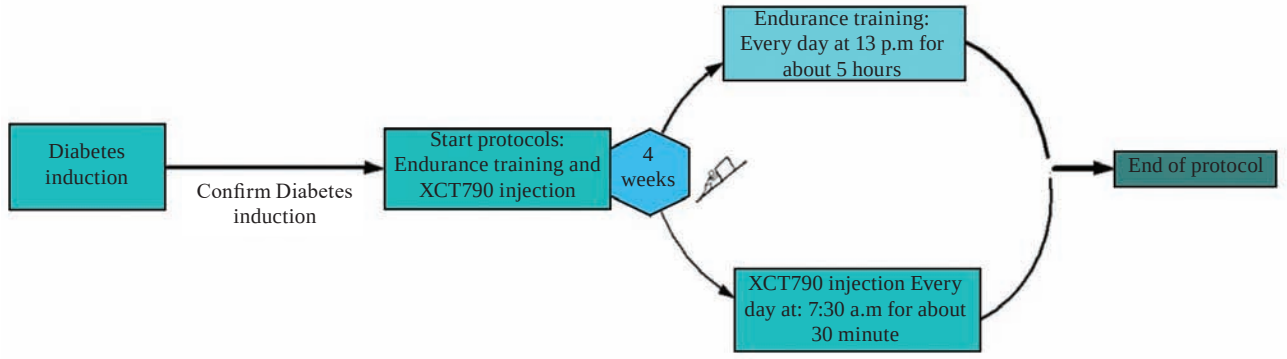

Diagram. Protocols and time points

forward and reverse primers (1 µl from each one), 100 ng of previously synthesized cDNA, and reaction volume reached to 20 µl by distilled water. The annealing temperature for each primer was adjusted according to its Tm. The thermal procedure was as follow; 95°C (5 min), 95°C (15 sec), annealing temperature (45 sec), 40 cycles. At the end of the Real-time PCR runs we defined the melt curve analysis. The 18S rRNA was used as a housekeeping and control gene and the relative expression of genes was determined by $2^{-\Delta\Delta Ct}$ method [34].

Statistical analysis. The analysis in this study was performed by SPSS version 22 and Sigma Plot version 12. The data were analyzed by two-way analysis of variance (Two-Way ANOVA) test and to pairwise comparisons; Tukey's method was used. Data are expressed as Mean±SEM. The *P* values < 0.05 were considered significant.

Results and Discussion

The combination of ERRα inhibition and ET in non-diabetic rats significantly increased MFN1 expression compared to non-diabetic control, ET, and non-diabetic rat with ERRα inhibition ($P < 0.001$). The combination of ERRα inhibition and ET in diabetic rats, significantly increased MFN1 expression compared to diabetic control, diabetic rats performed ET ($P < 0.001$), and diabetic rats with ERRα inhibition ($P = 0.002$) (Fig. 1).

The combination of ERRα inhibition+ET in non-diabetic rats significantly increased MFN2 expression compared to CTL ($P < 0.001$), ET ($P = 0.003$), and ERRI ($P = 0.012$) (Fig. 2). The combination of ERRα inhibition+ET in diabetic rats significantly increased MFN2 expression compared to D ($P < 0.001$) and diabetic+ET groups ($P = 0.012$). ET and ERRα inhibition in non-diabetic and diabetic rats increased MFN2 expression compared to non-diabetic and D groups ($P < 0.05$) (Fig. 2).

The combination of ERRα inhibition+ET in non-diabetic rats significantly increased GLUT2 expression compared to CTL ($P < 0.001$) and ET ($P = 0.01$). The combination of ERRα inhibition+ET in diabetic rats significantly increased GLUT2 expression compared to D and D+ET ($P < 0.001$), and D+ ERRI ($P = 0.01$) (Fig. 3).

Our results showed that ET significantly increased *PPARδ* gene expression compared to the CTL groups (non-diabetic and D controls) ($P = 0.001$) (Fig. 4). D+ET increased PPARδ ex-

Primers sequence which used in for real-time PCR gene expression measurement

Gene	Forward Sequence	Reverse Sequence
MFN1	TGGGGAGGTGCTGTCTCGGA	ACCAATCCCGCTGGGGAGGA
MFN	AGCGTCCTCTCCCTCTGACA	TTCCACACCACTCCTCCGAC
GLUT2	TAGTCAGATTGCTGGCCTCAGCTT	TTGCCCTGACTTCCTCTTCCAACT
PPARδ	GCCGCCCTACAACGAGATCA	CCACCAGCAGTCCGTCTTTGT
SCD1	AAAGTTTCTAAGGCCGCTG	GTCTGAGCCAGCAATCTCAA
18S	GCAATTATTCCCCATGAACG	GGCCTCACTAAACCATCCAA

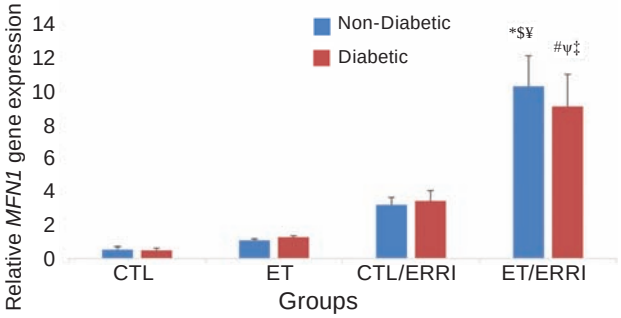

*Fig 1. Relative MFN1 gene expression quantified by Real-Time PCR method in liver of studied groups. *Statistically significant to non-diabetic group, #statistically significant to D group, $statistically significant to ET in healthy rats, ¥statistically significant to CTL+ERRI (Healthy animals which ERRα was inhibited), ψstatistically significant to ET in diabetic rats, ‡statistically significant to D+ERRI. Data are expressed as Mean±SEM. (P < 0.05 was considered as significant).*

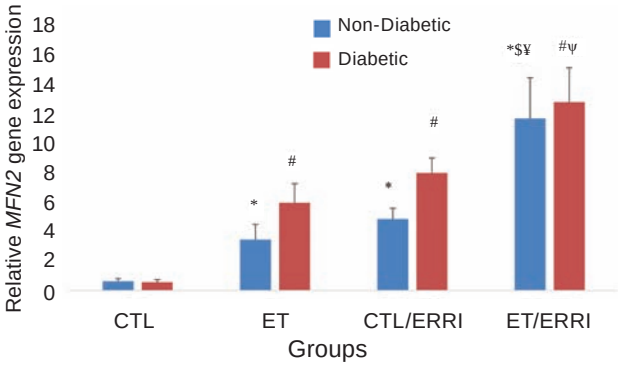

*Fig 2. Relative MFN2 gene expression quantified by Real-Time PCR method in liver of studied groups. *Statistically significant to CTL group, #statistically significant to D group, $statistically significant to ET rats, ¥statistically significant to CTL+ERRI, ψstatistically significant to D+ET, Data are expressed as Mean±SEM. (P < 0.05 was considered as significant).*

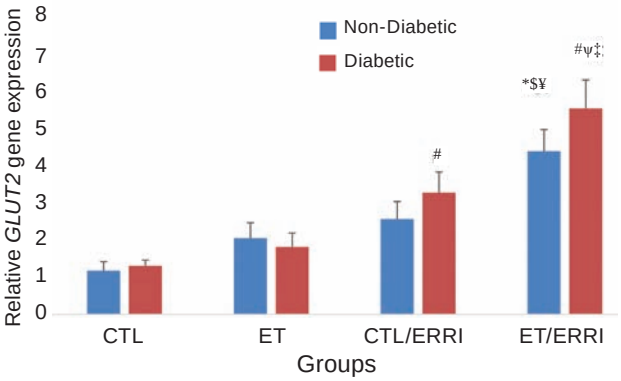

*Fig 3. Relative GLUT2 gene expression quantified by Real-Time PCR method in liver of studied groups. *Statistically significant to CTL group, #statistically significant to D group, $statistically significant to ET rats, ¥statistically significant to CTL+ERRI, ψstatistically significant to ET in D rats, ‡statistically significant to D+ERRI. Data are expressed as Mean±SEM. (P < 0.05 was considered as significant)*

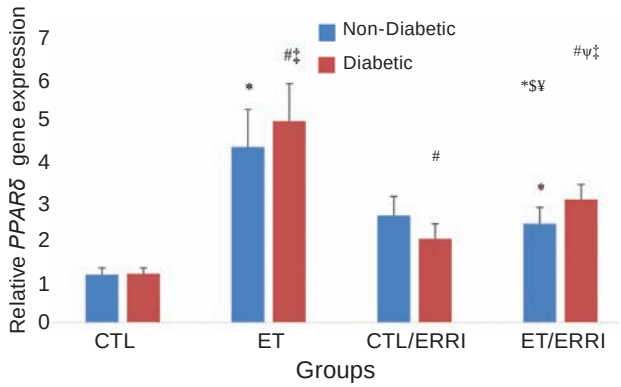

*Fig 4. Relative PPARδ gene expression quantified by Real-Time PCR method in liver of studied groups. *Statistically significant to CTL group, #statistically significant to D group, ‡statistically significant to D+ERRI. Data are expressed as Mean±SEM. (P < 0.05 was considered as significant)*

pression compared to D+ERRI (P = 0.002) and D+ET+ERRI (P = 0.061) (Fig. 4).

In D+ERRI group the SCD1 expression significantly increased compared to the DM and D+ET (P < 0.001), and D+ERRI+ET group (P = 0.001) (Fig. 5). The ERRα inhibition and the combination of ERRα inhibition+ET significantly increased SCD1 expression compared to CTL and ET groups (P < 0.001) (Fig. 5).

In the current study, we examined the ET and ERRα inhibition effects alone and in combination on the expression of genes involved in mitochondrial fusion and other genes that regulate lipid metabolism in non-diabetic and diabetic rats. Our results showed that ET significantly increased MFN2 and PPARδ expression in healthy and diabetic rats. ERRα inhibition in health and diabetic rats significantly promoted MFN2 and SCD1 expression. Finally, we

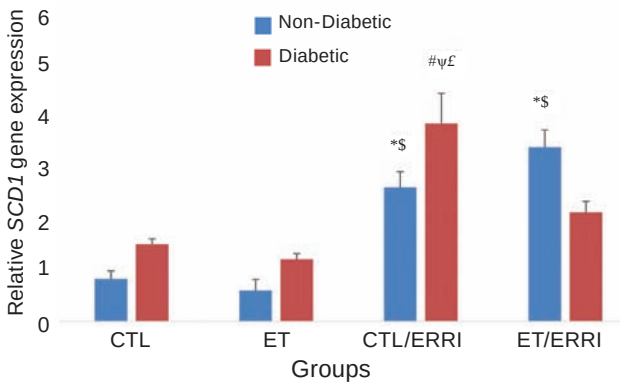

*Fig 5. Relative SCD1 gene expression quantified by Real-Time PCR method in liver of studied groups. *Statistically significant to CTL group, #statistically significant to D group, $statistically significant to ET in rats, ψstatistically significant to ET in DM rats, £statistically significant to D+ET+ERRI. Data are expressed as Mean±SEM. (P < 0.05 was considered as significant)*

found that a combination of ERRα inhibition with ET increased MFN1, MFN2 and GLUT2 expression.

ET is documented as a good alternative for diabetes management. ET elevated mitochondrial size and content and therefore promotes the oxidative capacity and reduces insulin resistance [4]. The proteins MFN1 and MFN2 are involved in mitochondrial dynamic [17]. It has been reported that down-regulated MFN2 activity and function in rat liver were correlated with metabolic disorder including diabetes and insulin resistance. Also, in patients with diabetes, MFN2 expression was reduced [18, 19]. Exercise is considered as an important factor that decreased mitochondrial imbalance and, Koo and Kong (2019) found that exercise on treadmill increased fusion proteins such as OPA1, MFN1 and MFN2 in the brain [20]. Soriano and colleagues have reported that improved insulin sensitivity after exercise training was related to MFN2 up-regulation [19]. Our results showed that ET significantly increased only MFN2, but not MFN1 expression in the liver of non-diabetic and diabetic rats that are the same with earlier studies, considering MFN2 and its beneficial effects in diabetes.

ERRα regulates glucose and lipid metabolism [9]. It has been reported that ERRα up-regulates *MFN2* gene expression [19]. Cartoni and coworkers showed that MFN2 expression is dependent on PGC-1α/ERRα and MFN2 is up-regulated by ERRα [4]. Unlike this, we found significant up-regulation of MFN2 (MFN1 was increased but this was not significant) in ERRI group. This MFN2 up-regulation in the presence of ERRα inhibition probably is dependent on its other roles rather than involving in mitochondrial fusion. But, the mechanism of this elevation is not clear. As well as, the group that has a combination of ET and ERRα inhibition, showed a significant increase in both MFN1 and MFN2 expression. We observed an additive effect between ET and ERRα inhibition to up-regulate MFN1 and MFN2 expression. These results also confirmed that MFN2 probably is more important in mitochondrial dynamic and function after ET, ERRα inhibition, and a combination of both.

GLUT2 facilitate glucose transportation into hepatocytes [10]. GLUT2 expression in diabetes was evaluated in several studies but the results were challenging [10-16]. In the current study, there was no significant difference over GLUT2 expression in non-diabetic and diabetic rats. It was reported that GLUT2 expression was increased in diabetic rats [10]. Sandoval-Muníz and colleagues (2018) showed that GLUT2 gene expression was increased in diabetic rats compared to the CTL group [14]. It has been reported that GLUT2 expression was increased in liver tissue of diabetic rats [16]. In fact, in our study GLUT2 expression showed a slight elevation in diabetic rats, and also in rats that performed ET (non-diabetic and diabetic), but these changes were not significant. On the other hand, Rathinam and Pari found that GLUT2 expression in the liver was reduced in STZ-induced diabetic rats [13]. Also, *GLUT2* gene and protein expression decreased in diabetic mice and rats and this reduction was related to glucose-stimulated insulin secretion [11, 12]. Our data are totally opposite in comparison with the studies that showed reduced GLUT2 expression. Disturbed glucose-induced insulin secretion correlated with GLUT2 down-regulation, and in diabetic models, increased Non-esterified fatty acid (NEFA) repress GLUT2 expression. But, it seems that because of tissue-specific regulation of GLUT2, it must reduce in pancreatic beta-cells but not in liver and this can justify our finding that we did not find any significant differences of GLUT 2 expressions in non-diabetic and diabetic rats in controls and ET groups [12]. ERRα inhibition in diabetic rats increased GLUT 2 expression, also a combination of ERRα inhibition plus ET up-regulated GLUT2 expression in both non-diabetic and diabetic rats. ET alone did not show significant effects on GLUT 2

expression, but in combination with ERRα inhibition, we found an additive effect of ET and ERRα inhibition on GLUT 2 expression in liver. ERRα null mice showed reduced blood glucose levels, and this GLUT2 up-regulation especially in diabetic rats can explain this phenomenon, and also confirm its beneficial effects in diabetic rats especially in combination with ET [9].

PPARδ modulates energy consumption in peripheral tissues and liver. Also, it improves insulin resistance, glucose homeostasis, and FAO [22, 23]. PPARδ expression was increased only after ET, but its changes were not significant in other groups. The change in substrates expenditure from glucose into FA is a marker of physical activity effects. Fan and coworkers found that PPARδ is related to ET in mice and PPARδ elevation significantly reduced glucose oxidation [25]. Our data are along with previous studies, and ET is related to PPARδ expression in non-diabetic and diabetic rats. Shortly, PPARδ agonist showed exercise mimetic effects, and this also confirmed our data that ET partially exerts its effects through PPARδ augmentation [25]. ERRα inhibition has no effect on PPARδ expression and also ERRα inhibition neutralized ET effect on PPARδ expression in groups that performed ET and ERRα was inhibited. ERRα increase FAO and mitochondrial oxidative phosphorylation and its inhibition significantly reduced PPARδ expression in diabetic rats. ET increased PPARδ expression but our results showing that in group of ERRI+ET, PPARδ expression we reduced. Therefore, probably ET effects on PPARδ exerted by ERRα and this effect was blocked by ERRα inhibition in ERRI+ET group.

Stearoyl CoA Desaturase 1 (SCD1) control and regulate monounsaturated FAs synthesis. SCD1 also is important for the production, storage, and movements of TG. SCD activity increased in diabetes and is correlated to obesity and cardiovascular disease (CVD) [26]. Our data also showed that SCD1 expression increased in diabetic rats compared to the health control group. Also, we found that ET has no significant effects on SCD1 expression in diabetic and non-diabetic rats. Shen et al found that SCD1 expression was increased after high-fat diet but not by exercise training [27] which was along with our results. Also, Yasari and colleagues reported that exercise training (8-week) attenuated SCD1 protein and gene expression in the liver [28]. ERRα inhibition (non-diabetic and diabetic group) increased SCD1 expression compared to control and ET counterparts. But, ET + ERRα inhibition significantly reduced SCD1 expression in diabetic rats that indicating ET blocks ERRα inhibition effects on SCD1 expression.

Conclusion. Considering the PPARδ expression pattern in this study, it seems that ERRα inhibition is not a good intervention in diabetic models because it undoes ET promoting effects on PPARδ expression. On the other hand, ERRα inhibition+ET increased MFN1 and especially MFN2 expression that indicates that it improve mitochondrial dynamic and function in the liver. ERRα inhibition+ET also increased GLUT2 expression in diabetic rats that helps to reduce blood glucose levels. It is necessary to focus on ERRα effects in diabetes to discover other aspects of this intervention's in diabetic models.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ВПЛИВ ФІЗИЧНИХ ТРЕНУВАНЬ ТА ІНГІБУВАННЯ ЕСТРОГЕННОГО РЕЦЕПТОРА АЛЬФА НА ЕКСПРЕСІЮ МІТОФУЗИНУ 1 І 2, GLUT2, PPARβ/δ І SCD1 У ПЕЧІНЦІ ДІАБЕТИЧНИХ ЩУРІВ

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Діабет – прогресуюче метаболічне захворювання, широко поширене у всьому світі. Фізична активність вважається одним із засобів для поліпшення стану за діабету. Одним із нових підходів до лікування цукрового діабету є інгібування естрогензв'язаного рецептора α (ERRα). У роботі вивчали вплив одночасного інгібування ERRα та фізичного тренування на експресію генів мітофузину 1 (MFN1), MFN2, транспортеру глюкози 2 (GLUT2), β- і δ-рецепторів, що активуються пероксисомними проліфераторами (PPARβ/δ) і стеароїл-КоА-десатурази 1 (SCD1) в печінці щурів. Щурів було розділено на 8 груп (n = 7): 1 – контроль (CTL); 2 – діабетичні щури (D); 3 – інгібування ERR (ERRI); 4 – тренування на витривалість (ET); 5 – діабетичні щури + інгібування ERR (D+ERRI); 6 – діабетичні щури + тренування на витривалість (D+ET); 7 – тренування на витривалість + інгібування ERR (ET+ERRI); 8 – діабетичні щури + тренування на витривалість + інгібування ERR (D+ET+ERRI). Тканини печінки використовували для ПЛР-тесту в реальному часі. Показано, що фізичне навантаження значно підвищувало експресію PPARδ, MFN1 та MFN2 в контрольних щурів порівняно з групою D. У групі ERRI експресія генів *SCD1*, *GLUT2*, *MFN1* та *MFN2* підвищувалась порівняно з групою CTL та D. У щурів груп CTL та D одночасне застосування інгібування ERRα та фізичного навантаження істотно збільшувало експресію MFN1, MFN2 та GLUT2. Дійшли висновку, що поєднання фізичних тренувань та інгібування ERRα, можна розглядати як потенційний терапевтичний метод для лікування метаболічних захворювань, зокрема діабету та серцево-судинних захворювань.

Ключові слова: діабет, естрогенний рецептор α (ERRα), транспортер глюкози, мітофузин, рецептори, що активуються пероксисомними проліфераторами (PPARβ/δ), стеароїл-КоА-десатураза (SCD1).

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