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EFFECT OF MODERATE SWIMMING EXERCISE WITH A DIETARY VITAMIN D ON SERUM IRISIN LEVEL IN DIABETIC RATS

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Effect of Moderate Swimming Exercise with a Dietary Vitamin D on Serum Irisin Level in Diabetic Rats.

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ABSTRACT

Background: Irisin is a recent myokine that decreases obesity and enhances insulin resistance by converting white adipose tissues to brown, leading to increase thermogenesis and lower insulin resistance.
Aim of the study: The impact of moderate swimming exercise combined with dietary vitamin D on serum irisin levels was evaluated in a type II diabetes mellitus (T2DM).
Material and Methods: This study was conducted between September and December 2020 on 50 male adult albino rats at animal house of physiology department, Al-azhar university. Rats have been split into 5 equal groups: Group I was the control group, Group II was the diabetic control group, Group III was the diabetic exercise group, Group IV was the diabetic group that received vitamin D, and Group V was the diabetic exercise group that received vitamin D. Serum was collected after the experiment to determine glucose, insulin, resistance to insulin, irisin levels, and lipid profiles.
Results: Diabetic rats exhibited hyperglycemia, hyperlipidemia, and high insulin resistance accompanied by significant hypoinsulinemia, and low serum irisin level. The results also showed that moderate swimming exercise and vitamin D supplementation improved serum level of irisin, glucose, insulin, insulin resistance, and lipid profile (Cholesterol, LDL, and triglycerides) in diabetic rats. The combination of vitamin D and moderate swimming gives the best effects.
Conclusion: Vitamin D supplementation with moderate exercise is very beneficial to diabetic patients. Irisin can be used later on as a biomarker for insulin resistance as it had a strong negative association with it.

Keywords: *Diabetes; Irisin; Insulin; swimming exercise; vitamin D*

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INTRODUCTION

T2DM is one of the most frequent metabolic disorders in the world, and it is mainly induced via a mixture of two key factors: defective insulin secretion through pancreatic β-cells and insulin-sensitive tissue failure. [1] Insulin must precisely satisfy metabolic requirements. As a result, the molecular mechanisms governing insulin synthesis, release, and tissue insulin response must all be closely regulated. So, any disorder in mechanisms that cause a metabolic imbalance that results in T2DM can occur. [2] Skeletal muscle is an endocrine organ that released myokines proteins that are involved in modulating many of the positive effects of exercise on cell metabolism. [3] Myokines have a strong role in preventing the development of DM due to their ability to promote glucose uptake and lipolysis. One such myokine, irisin, has been shown to convert white adipose tissue to brown. [4]

Exercise stimulates the expression of the protein fibronectin-type III domain-containing 5 (FNDC5), which is an irisin precursor, by increasing the expression of peroxisome proliferator-activated receptor-γ (PPAR- γ). Irisin prompts the expression of uncoupling protein 1 (UCP1) in adipose tissue which transforms white adipocytes to brown adipocytes. [5] The conversion of white fat to brown one increases energy expenditure and thermogenesis that increase insulin sensitivity and decrease its resistance. Abnormalities in irisin have been linked to the pathogenesis of metabolic diseases like DM. [6]

It was reported that serum irisin level was decreased in a diabetic patient. Interventions that modulate irisin levels and return them to healthy levels may

offer an effective therapeutic approach for treating DM. [7]

Vitamin D (cholecalciferol) is a fat-soluble vitamin with a well-known role in bone health and Ca^{+2} metabolism. In hypovitaminosis D, the synthesis and secretion of insulin have been reported to be impaired. Epidemiological studies suggested a connection between vitamin D deficiency in early life and the later onset of T1DM and T2DM. [8] Vitamin D has been reported to affect the growth and function of muscle tissues, and be involved in improving glucose metabolism. [9] Researchers have reported an interaction between the vitamin D receptor (VDR) and PGC-1α. Additionally, vitamin D activates p38/MAPK (mitogen-activated protein kinase) in muscle. PGC-1α and irisin are regulated by the activation of p38/MAPK. [10] Swimming is a common model for assessing the impact of aerobic activity in physiological and pathological conditions in rats. Regular physical activity has been proposed as a means of preventing or delaying the onset of diabetes and its complications. Healthy and diabetic people are advised to engage in 150 minutes of moderate-intensity aerobic activity each week to maintain their wellbeing. [11]

The current research looked into the effect of moderate swimming exercise with a dietary vitamin D on serum irisin level in diabetic rats and the correlation between irisin and glucose, insulin, IR, and lipid profile.

MATERIAL AND METHODS

This study was conducted between September and December 2020 at animal house of physiology department, Al-azhar university.

Animals: The animal model for this research was 50 male adult albino rats from a local strain. They were kept in suitable cages (30x32x30 cm for every five rats) at room temp and on a natural light/dark cycle. They weighed 110 -130 g. They were fed standard food as well as bread and green vegetables and were given unlimited access to water. Before the experiment, they were held for 10 days to adapt to their new environments.

Drugs and Chemicals: Sigma-Aldrich Co., St Louis, USA provided the streptozotocin (STZ) and rat irisin ELISA kits. Egypt's local pharmacy provided vitamin D.

Study design: Five equal groups of rats were created:

Group I (Normal control group): Provided with standard animal pellet and water.

Group II (Diabetic control group): Using HFD/STZ model.

Group III (Diabetic exercised group).

Group IV (Diabetic group received vitamin D): The diabetic rats were given 500 IU/kg vitamin D per day via oral gavage. [12]

Group V (Diabetic exercised group received vitamin D): The diabetic rats underwent exercise training for 6 weeks and received vitamin D

Induction of diabetes: Diabetes was induced on day zero of the present study. Type II DM was induced experimentally using HFD/STZ protocol as described in a previous study. [13] Briefly, a two-week high-fat diet (HFD) was followed by a single intraperitoneal injection of STZ (35 mg/kg body weight).The level of blood glucose has been determined by drawing entire blood from the tail vein on day 5 after STZ administration. Rats with blood glucose levels >200 mg/ dl were considered diabetic. An Accu-Chek glucometer was used to measure blood glucose levels (Roche, Germany).

Moderate swimming exercise protocol: Rat in exercise groups were subjected to a swimming program in a swimming plastic barrel (80 cm long, 50 cm wide, and 90 cm deep), and swimming training has always been done individually in water that was 31±1ºC, between 10 to 12 h a.m. On the first day, rats were allowed to stay in the water for 10 min till they could swim for 60 minutes per session at the end of the first week. The exercise protocol was continued for 5 weeks (5 times per week; 60 minutes per session) [(14)].

Biochemical parameters in blood: Rats fasted for 12 hours after the experiment, and samples of blood were obtained from the retro-orbital venous plexus through a heparinized capillary tube. The blood samples were held in centrifuge tubes till they coagulated, then centrifuged for 15 minutes at 5000 rotations per minute to separate the serum. The serum has been sucked into Eppendorf tubes and frozen at -20 ºC till it was used to estimate blood glucose level [15], insulin [16], insulin resistance using homeostasis model assessment of insulin resistance (HOMA-IR)[17] serum irisin levels, [3] lipid profile (triglycerides "TG" [18] total cholesterol "TC" [19], low-density lipoprotein "LDL" [20] and high-density lipoprotein "HDL". [21]

Statistical analysis

The information was provided in the form of a mean ± SD. For the statistical analysis, SPSS software version 20 (IBM Co., USA) has been used to perform ANOVA followed by post-hoc-test (LSD), with $P \leq 0.05$ indicating a statistically significant difference. Pearson correlation has been used to test the importance of correlation among two quantitative variables, with its t-test.

RESULTS

Regarding the irisin level, STZ-induced diabetes rats had a significantly lower irisin level than the control

group (p<0.05). Serum irisin levels increased significantly in diabetic rats those participated in swimming programs or received vitamin D alone or in combination, relative to the diabetic group (p<0.001). In contrast, there was no difference noticed in the irisin level between the diabetic rats which underwent exercise training for 6 weeks, and diabetic rats that received vitamin D (p>0.05). When diabetic rats received vitamin D and underwent exercise training in combination, Serum irisin levels markedly increased than those from each one separately. (p<0.05) (Table 1).

Concerning glucose and insulin level, diabetic rats exhibited marked higher blood glucose and lower insulin levels (p<0.001) when compared to normal control rats. Nevertheless, when diabetic rats practiced swimming programs or received vitamin D alone or in combination, serum level of glucose decreased, and insulin increased significantly as compared to diabetic rats (p<0.05, p<0.05, and p<0.001). Between diabetic exercised rats and diabetic rats those received vitamin D, however, there was no difference in glucose or insulin levels (p>0.05). The level of glucose and insulin were significantly improved in diabetic exercised rats those received vitamin D than diabetic exercised rats or diabetic rats received vitamin D (p<0.05) (Table 1).

Concerning insulin resistance (IR), in diabetic rats, it rose significantly more than in normal control rats (p<0.001). However, when diabetic rats practiced swimming programs or received vitamin D alone or in combination, their IR reduced significantly as relative to diabetic rats (p<0.001, p<0.05, and p<0.001). Insulin resistance was not different among diabetic exercised rats and diabetic rats were given vitamin D (p>0.05). Insulin resistance was significantly lower in diabetic exercised rats those received vitamin D than in diabetic exercised rats or diabetic rats received vitamin D. (p<0.05) (Table 1).

Concerning Pearson correlation among serum levels of irisin and glucose in different diabetic groups; in the diabetic control group, serum irisin levels were moderately negatively correlated with serum glucose levels (r= -0.686, p<0.05), strong negative correlation in both diabetic exercised group, diabetic rats received vitamin D and diabetic exercised rats received vitamin D (r= -0.838, p<0.05; r= -0.854, p<0.05; r= -0.973, <0.001 respectively) (Table 2).

About Pearson correlation among serum irisin levels and insulin in different diabetic groups; there were strong positive correlation in diabetic control rats and diabetic exercised rats received vitamin D (r= 0.958, p<0.001; r= 0.947, p<0.001 respectively). The association were moderate in diabetic exercised group and diabetic rats received vitamin (r = 0.676, p<0.05; r = 0.658, p<0.05 respectively) (Table 2).

Concerning the Pearson relation among serum levels of irisin and IR in various diabetic groups, all diabetic groups had a strong negative association among serum irisin and IR levels (diabetic control group: r = -0.862, p<0.05; diabetic exercised group: r =- 0.946, p<0.001; diabetic rats received vitamin D: r = -0.938, p<0.001; diabetic exercised rats received vitamin D: r = -0.919, p<0.001) (Table 2).

Groups	**Irisin (ng/ml)**	**Glucose (mg/dl)**	**insulin (µIU/ml)**	**HOMA-IR**
Group (I): Normal Control rats	11.8 ±0.57	127.6±9.1	10.8±1.002	3.39 ±0.39
Group (II): Diabetic control rats	8.74±0.66*	277.5±13.36*	8.11±0.63*	5.56±0.55*
Group (III): Diabetic exercised rats	11.42±1.12†	244.2±15.71†	7.21±0.62†	4.35±0.50†
Group (IV): Diabetic rats received vitamin D	12.07±0.88†	255±8.76†	7.42±0.95†	4.67±0.46†
Group (V): Diabetic exercised rats received vitamin D	14.02±0.70†®■	228±19.33†®■	6.11±0.61†®■	3.44±0.49†®■

Table 1: Effects of vitamin D supplementation and exercise on serum irisin (ng/ml), glucose (mg/dl), insulin (µIU/ml), and HOMA levels in the various experimental groups (Mean±SD).P* vs. control group; P† vs. diabetic control group. P® vs. Diabetic exercised group P■ vs. Diabetic group received vitamin D. HOMA, homeostasis model assessment of insulin resistance; SD, standard deviation.

Groups / **Parameters**	**Group (II)**		**Group (III)**		**Group (IV)**		**Group (V)**	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Glucose (mg/dl)	-0.688	<0.05	-0.837	<0.05	-0.815	<0.05	-0.932	<0.001
Insulin(µIU/ml)	0.947	<0.001	0.665	<0.05	0.637	<0.05	0.833	<0.001
HOMA IR	-0.868	<0.05	-0.955	<0.001	-0.913	<0.001	-0.919	<0.001

Table 2: Pearson correlation among serum Irisin level and (Glucose, insulin, and HOMA IR) in all diabetic groups. r = correlation coefficient; p= probability value and HOMA-IR: Homeostasis model assessment of insulin resistance.

Concerning blood cholesterol level, diabetic rats had a higher level ($p<0.001$) than normal control rats. However, comparing diabetic rats to diabetic rats practicing swimming programs or receiving vitamin D separately or in combination, the serum level of cholesterol reduced significantly ($p<0.05$, $p<0.05$, and $p<0.001$ respectively). Between diabetic exercised rats and diabetic rats which received vitamin D, there has been no difference in cholesterol level. By comparing diabetic exercised rats receiving vitamin D with diabetic exercised rats, or with diabetic rats receiving vitamin D, serum cholesterol level decreased significantly ($p<0.05$). (Figure 1).

Regarding the blood TG level, diabetic rats had higher levels than normal control rats ($p<0.001$). Likewise, when diabetic rats compared to diabetic rats those practiced swimming programs or received vitamin D separately or in combination, the serum level of TG decreased significantly ($p<0.05$, $p<0.05$, and $p<0.001$ respectively). In contrast, no difference was noticed in TG level among diabetic exercised rats and diabetic rats which received vitamin D. The level of TG decreased markedly in diabetic exercised rats receiving vitamin D than diabetic rats receiving vitamin D without exercise ($p<0.05$). The level of TG decreased insignificantly in diabetic exercised rats receiving vitamin D than diabetic rats which underwent exercise without vitamin D ($p>0.05$) (Figure 1).

Regarding the blood HDL level, streptozotocin-induced diabetic rats had significantly lower HDL levels than normal control rats ($p<0.001$). However, when diabetic rats practiced swimming programs or received vitamin D alone or in combination, the serum HDL level increased markedly when compared to the diabetic group ($p<0.05$). No difference in HDL level between the diabetic exercised rats and diabetic rats receiving vitamin D ($p>0.05$). When diabetic rats received vitamin D and underwent exercise training in combination, the serum HDL level increased significantly than those from each one separately ($p<0.05$) (Figure 1).

Regarding the blood LDL level, it increased markedly in diabetic rats than normal control rats ($p<0.001$). Even so, when diabetic rats were compared with diabetic rats those practiced swimming programs or received vitamin D separately or in combination, the serum level of LDL decreased significantly ($p<0.001$, $p<0.05$, and $p<0.001$ respectively). There was an insignificant difference in LDL level among diabetic exercised rats and diabetic rats that received vitamin D. The level of LDL decreased markedly in diabetic exercised rats receiving vitamin D than diabetic rats receiving vitamin D without exercise ($p<0.05$). LDL decreased insignificantly in diabetic exercised rats receiving vitamin D than diabetic rats who underwent exercise without vitamin D supplementation ($p>0.05$) (Figure 1).

Concerning the Pearson association among irisin serum levels and cholesterol in different diabetic groups; there were srong negative association among serum irisin level and cholesterol level in all diabetic groups (diabetic control group: $r = -0.959$, $p<0.001$; diabetic exercised group: $r = -0.827$, $p<0.05$; diabetic rats received vitamin D: $r = -0.961$, $p<0.001$; diabetic exercised rats received vitamin D: $r = -0.922$, $p<0.001$) (Table 3).

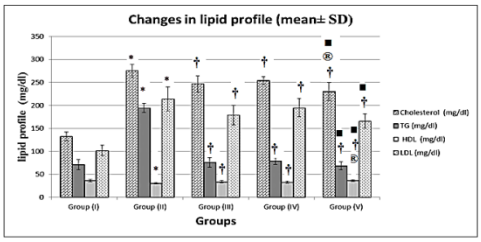

Fig 1: Effects of vitamin D supplementation and exercise on serum Cholesterol (mg/dl), TG (mg/dl), HDL (mg/dl), and LDL(mg/dl), levels in the various experimental groups (Mean±SD). P^{*} vs. control group; $P^{\dagger}$ vs. diabetic control group. $P^{®}$ vs. Diabetic exercised group $P^{■}$ vs. Diabetic group received vitamin D. TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

About the Pearson association among serum irisin levels and TG in different diabetic groups; there were srong negative association among serum irisin leve and TG level in all diabetic groups (diabetic control group: $r = -0.877$, $p<0.05$; diabetic exercised group: $r = -0.851$, $p<0.05$; diabetic rats received vitamin D: $r = -0.952$, $p<0.001$; diabetic exercised rats received vitamin D: $r = -0.934$, $p<0.001$) (Table 3).

Concerning the Pearson association among serum levels of irisin and HDL in different diabetic groups; there were strong positive association among serum irisin leve and HDL level in all diabetic groups (diabetic control group: $r = -0.786$, $p<0.05$; diabetic exercised group: $r = -0.779$, $p<0.05$; diabetic rats received vitamin D: $r = -0.933$, $p<0.001$; diabetic exercised rats received vitamin D: $r = -0.935$, $p<0.001$) (Table 3).

About the Pearson association among serum irisin levels and LDL in different diabetic groups; there were srong negative association among serum irisin leve and LDL level in all diabetic groups (diabetic control group: $r = -0.944$, $p<0.001$; diabetic exercised group: $r = -0.863$, $p<0.05$; diabetic rats received

vitamin D: r = -0.822, p<0.05; diabetic exercised rats received vitamin D: r = - 0.949, p<0.001) (Table 3).

Groups / Parameters	Group (II)		Group (III)		Group (IV)		Group (V)	
	r	p	r	p	r	p	r	p
Cholesterol(mg/dl)	-0.959	<0.001	-0.827	<0.05	-0.961	<0.001	-0.922	<0.001
TG (mg/dl)	-0.877	<0.05	-0.851	<0.05	-0.952	<0.001	-0.934	<0.001
HDL (mg/dl)	0.786	<0.05	0.779	<0.05	0.933	<0.001	0.935	<0.001
LDL (mg/dl)	-0.944	<0.001	-0.863	<0.05	-0.882	<0.05	-0.949	<0.001

Table 3: Pearson correlation among serum irisin level and lipid profile (Cholesterol, TG, LDL, and HDL) in all diabetic groups. r=correlation coefficient; p= probability value.

DISCUSSION

The diabetic sedentary group had significantly lower serum irisin levels than the control group, according to the results of this study. This result was in agreement with a previous study [22] which detect a decreased serum level of irisin in type II diabetic rats compared to control one. Also, other studies [23,24] found a significant decline in irisin concentration in adults with type II DM, and they attributed these findings to skeletal muscle insulin resistance that changes irisin expression and secretion or impaired irisin secretion which has a role in insulin resistance. [25] The present study was in controversy with the result of other studies [26,27] that showed a significantly higher irisin level in diabetic patients than healthy ones, and they explained that DM type II is related to increased irisin release to compensate for the insulin resistance observed in skeletal muscle.

Irisin therapy increases uncoupling protein1 (UCP1) via increased phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) and regulatory kinases, according to a study [28] published in 2014 to explicate the molecular mechanisms of irisin action. Irisin is suggested as a hormone capable of raising energy consumption, enhancing weight loss, and reducing insulin resistance in this way. [29]

In our study, moderate swimming exercise produced a significant rise in serum level of irisin compared to the diabetic sedentary group. This agreed with the results of a study in 2015 which measured irisin serum level in response to exercise in type II diabetic humans and reported an increase in irisin level in response to exercise. [30] Physical activity increased the expression of peroxisome proliferator-activator receptor co-activator (PGC) 1, a downstream membrane protein, as well as fibronectin type III domain-containing 5 (FNDC5), that is cleaved to form irisin in skeletal muscle, according to the former study. [31] The researchers identified adipose tissue as the primary source of circulating irisin in these patients, which contradicted the results of preceding studies that showed increased levels of circulating irisin in extremely obese sedentary ladies, and the serum irisin levels were associated with body mass index (BMI) and fat mass. These controversies may be due to the difference in type and duration of exercise that can affect the expression of (Peroxisome proliferator-activated receptor-gamma-coactivator-1-alpha) or FNDC5. [32,33]

In our study, There was an increase in irisin level in diabetic rats that received vitamin D alone or in combination with swimming training than a sedentary diabetic rat. This result agreed with another study that detected a rise in irisin levels in diabetic rats' serum after vitamin D supplementation alone or in combination with exercise. [23] A study in 2014 studied the effect of a single vitamin D dose of 100,000 IU and did not observe any change in circulating irisin level. This discrepancy may be related to that; they gave a single shot of a high dose of vitamin D which might not be enough to affect the circulating irisin. [7]

The current study showed that exercised diabetics had lower plasma glucose levels than sedentary diabetics. This result corroborated a previous study that found that daily physical exercise improves diabetic patients' physical strength, regulates blood glucose, and avoids the progression from reduced glucose tolerance to type II diabetes mellitus. Physical activity causes fatty acid oxidation as well as an increase in insulin sensitivity in the liver, leading to lower glucose production and output in the existence of insulin. [3] Also, a study was done on type II diabetic mice models after six weeks of aerobic exercise, improve HbA1c, HOMA-IR, and higher insulin sensitivity. [34]

In our study, diabetic rats who received vit D had lower blood glucose levels and higher insulin levels than sedentary diabetic rats. This agreed with former studies which found that supplementing with vit D in type II DM with defective insulin secretion improved β cell activity and corrected the defect, implying that vit D may play a role in improving insulin secretion and sensitivity. [35,36] A previous study showed that

vitamin D administration on diabetic rats improved hyperglycemia and insulin sensitivity by the increased expression of vit D receptor (VDR) in pancreatic β-cells. [37] Vitamin D may have an indirect effect on insulin resistance like which occur through beneficial effects on adiposity. [38]

In our study, serum irisin levels were found to have a negative association with glucose or HOMA-IR and a positive correlation with insulin in all diabetic groups. This agreed with the result of a previous study [39] that recorded a negative association among irisin level and HOMA-IR in type II diabetes rats model, but the result was not in agreement with another study that observed a positive association among irisin and fasting blood glucose and HOMA-IR in women of normal weight and women with diabetes. [32,40] The positive correlation was due to an increased serum level of irisin, which encourages energy consumption, resulting in weight loss, fat reduction, and enhanced insulin resistance. [41]

Sedentary diabetic rats had significantly higher serum cholesterol, triglycerides, LDL, and decreased HDL levels than swimming-trained diabetic rats or diabetic rats receiving vitamin D alone or in combination with swimming training in the present research. A previous study reported that hypovitaminosis D has been linked to a higher risk of dyslipidemias, they also reported that vitamin D deficient patients have higher triglyceride and lower HDL-C values than vitamin D sufficient ones. [42] The previous study's findings showed a significant increase in HDL after using vitamin D supplements in controlled clinical trial studies in humans. [43] Oral vit D supplementation is an efficient method for lowering triglycerides, cholesterol, and LDL, according to a study published in 2019. [44] Another potential explanation for the connection among 25(OH) D and lipid profile is insulin resistance. When vit D deficiency exists, the risk of insulin resistance rises, which is linked to a rise in VLDL cholesterol and triglyceride levels. [45] A previous study found no connection between serum 25(OH) D levels and lipid profile. This discrepancy may be related to the difference in hormonal sensitivity between people which could affect lipid metabolism differently. In addition, lifestyle differences like smoking, alcohol intake, exposure to sunlight, and physical exercise, can affect lipid metabolism. [46]

The present study was in agreement with a previous study that detected lower plasma LDL-C and TC levels higher HDL-C levels after four weeks of exercise in rats. [47] Our findings differed from those of previous studies which reported reduced HDL levels after an exercise activity. [48] Although a few studies reported that exercise activity has an insignificant impact on HDL levels, abundant studies reported an increase of HDL level after exercise activities. [49]

There was a negative association among the level of the irisin and lipid profile (cholesterol, TG, and LDL) in the present study, but a positive correlation with HDL in the studied groups which means that the level of irisin can affect the lipid profile and considering it to be protective against hyper-lipidemia. A study in 2014 [50] found that the decreased irisin level in obese diabetic adults was linked to a higher risk of hyperlipidemia and hyperglycemia, while, another study demonstrated that people with type II diabetes and hyperlipidemia had higher concentrations of irisin. [51] A former study proved a negative correlation between irisin and lipid profile (cholesterol & triglycerides) in different athletics groups, suggesting that this hormone can play a role in metabolic regulation mechanisms. [52] The predicted beneficial effect of irisin on lipid profile was focused on the “browning” of white or beige adipose tissue into brown adipose tissue caused by irisin [(53)].

CONCLUSION

Vitamin D supplementation with moderate exercise training is beneficial in T2DM as that combination partially corrected the reduction in serum irisin and insulin levels. Moreover, irisin level can be used later on as a biomarker for insulin resistance as it had a significantly strong negative correlation with HOMA-IR.

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