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RESEARCH ARTICLE

THE ROLE OF EXERCISE AND / OR IRISIN IN CASES OF HYPOTHYROID MALE RATS

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Abstract

The aim of the work: The aim of this work is to evaluate the role of exercise and / or irisin in cases of hypothyroid male rats

Material and Methods: 90 local strain male rats divided into two groups: Group 1-Without exercise which is divided five subgroups 10 rats each, Subgroup Ia Euthyroid Control rats receive 0.5 ml physiological saline daily intraperitoneal (IP) for 3 weeks. Subgroup. IIa Hypothyroid Control rats will be injected by 6-n-propyl-2thiouracil (PTU) with a dose 10 mg/kg/day (IP) for 3 weeks. subgroup IIIa L-Thyroxine Treated Hypothyroid rats: Induction of hypothyroid as in group IIa then will receive L-Thyroxine hormone (IP) with a dose of 1.5mg /kg/day for 10 days. Subgroup VIa Irisin Treated Hypothyroid rats: Induction of hypothyroid as in subgroup IIa then will receive Irisin hormone (IP) with a dose of 10µg/kg/day for 10 days. subgroup Va Irisin & L-Thyroxine treated hypothyroid rats Induction of hypothyroid as in subgroup 2a then will receive Irisin hormone as in subgroup 4a and L-Thyroxine as in subgroup 3a for 10 days. Group 2-With Acute Forced Swimming which is divided into five subgroups 10 rats each Subgroup Ib: Euthyroid Control Acute Forced Swimming subgroup: will be treated as subgroup 1a then will be submitted to acute forced swimming .Subgroup II b: Hypothyroid Acute Forced Swimming treated as in subgroup IIa then will be submitted to acute forced swimming. Subgroup III b: Thyroxine treated hypothyroid acute forced swimming subgroup: treated as in subgroup II a, then will be submitted to acute forced swimming then will receive L-Thyroxine as in subgroup IIIa. Subgroup IV b: Irisin treated hypothyroid acute forced swimming group: treated as subgroup II a, then will be submitted to acute forced swimming then will receive Irisin similar to subgroup IVa. For all these rats, For group 2, the Maximal Swimming Time (MST) were measured then for all animal studied the body weight, body mass index and abdominal circumference were measured one day before and at the end of experimental period. Tri-iodothyronine (T3), Thyroxin (T4), Thyroid Stimulating Hormone (TSH), Irisin and Creatin Kinase (CK) were measured also lipid profile will be measured Triglycerides, cholesterol, LDL, HDL and phospholipids.

Results: In hypothyroid rats, irisin injection only caused decrease in body weight, abdominal circumference and body mass index with decrease

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in lipid profile but no improvement in thyroid function tests. While L-thyroxine injection only caused improvement in thyroid function tests but no significant improvement in anthropometric measurements and lipid profile. On the other hand, injection of both irisin and L-thyroxine gave the best results in all parameters as both improved anthropometric measurements, lipid profile and thyroid function tests. hypothyroid animal had significant increase in serum CK levels as compared to normal euthyroid rats. L-thyroxine when given as treatment to hypothyroid rats caused significant reduction in CK. However, when irisin was given as a treatment to hypothyroid animals, it caused more increase in irisin than hypothyroid rats. Acute exercise causes significant decrease in MST in hypothyroid animals and those treated with irisin as compared to control and those of hypothyroid treated with thyroxine. However, Acute exercise caused no significant change in all other parameters studied.

Conclusion: Irisin has a major role in reducing weight by converting white fat tissue into brown adipose tissue and then to heat. On the other side of the study, irisin has no direct effect on improving the secretion of thyroid hormones in people with thyroid hormone deficiency. Also, the injectable exogenous irisin has a better and more potent effect than the endogenous irisin resulting from acute short-term exercise.

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Introduction:-

Irisin a myokine known as a muscle-secreted factor promoting browning of adipose tissue in mice. (Bostrom et al., 2012) (Aydin et al., 2013) the peroxisome proliferator-activated receptor α coactivator 1 (PGC 1) expression in muscle as a result of exercise stimulates an increase in expression of the fibronectin type III domain-containing protein 5 (FNDC 5 Gene) which encode a type I membrane protein that is processed proteolytically to form irisin a hormone secreted into blood. (Matsuo et al., 2015). The changes of irisin in response to exercise remain to be investigated (Kraemer et al., 2014). Some describe an increase irisin after acute exercise (Norheim et al., 2014) or after chronic exercise program (Lawson et al., 2014), whereas others failed to verify these results. (Pekkala et al., 2013)

Thyroid functions could directly or indirectly be related to irisin regulation or vice versa irisin could affect the thyroid. (Gouni-Berthold et al., 2013).

Studies on irisin level with regard hypothyroidism are controversial irisin concentration was lower in patients with prolonged hypothyroidism (Zybek-Kocik et al., 2017). However, Grigorios et al., 2016 concluded that changes in thyroid axis hormone levels do not affect circulating irisin levels. On the other hand, irisin levels increase significantly in hypothyroidism. (Emine et al., 2017) (Samy et al., 2015)

In the present study, we investigated the role of exercise and / or irisin in cases of hypothyroid male rats.

Materials and Methods:-

Experimental design:

This work will be carried out on 90 local strain adult male rats (approximate body weight 150- 200 gm). Rats will be housed with free access to laboratory chow and tap water. The animals will be kept at room temperature 22-24 °C. All procedures will be done according to the ethical committee of Faculty of Medicine, Tanta University. The animals will be randomly divided into 2 groups:-

Group 1 without exercise subdivided into 5 subgroups (10 rats each):

Subgroup Ia:

Euthyroid Control Group (EC):

will receive 0.5 ml physiological saline daily intraperitoneal (IP) for 3 weeks.

Subgroup IIa:**Hypothyroid Control Group (HC):**

will be injected IP by 6-n-propyl-2 thiouracil (PTU) at a dose of 10 mg/kg/day for 3 weeks for induction of hypothyroidism. (serum Free T3 reach 0.24 ± 0.12 pg/ml, serum Free T4 reach 0.22 ± 0.01 ng/dl, serum TSH reach 8.5 mIU/L (Mogulkoc et al., 1999), (Samy et al., 2015).

Subgroup IIIa:**L-Thyroxine Treated Hypothyroid Subgroup (L-Thyroid ttt H):**

will receive (PTU) for 3 weeks, then these animals will receive L-Thyroxine hormone (IP) at a dose of 1.5 mg/kg/day for 10 days. (Aydin et al., 2010)

Subgroup VIa: Irisin Treated Hypothyroid Group (Irisin ttt H):

will receive (PTU) for 3 weeks, then these animals will receive Irisin hormone (IP) in a dose of day as $10\mu\text{g}/\text{kg}/\text{day}$ for 10 days. (Jinjuan et al., 2016)

Subgroup Va:**Irisin & L-Thyroxine Treated Hypothyroid Group (Irisin & L-Thyroxine ttt H):**

will receive (PTU) for 3 weeks, then these animals will receive Irisin hormone and L-Thyroxine hormone for 10 days.

Group 2 without exercise subdivided into 5 subgroups (10 rats each):**Subgroup Ib :****Euthyroid Control Acute Forced Swimming Group (CS):**

will receive physiological saline daily then these animals will be submitted to acute forced swimming to measure the maximal swimming time (MST) test once. (Matsakas et al., 2006)

SubgroupI Ib :**Hypothyroid Acute Forced Swimming Group (HS):**

will receive (PTU) for 3 weeks, then these animals will be submitted to acute forced swimming to measure the MST test once

Subgroup IIIb :**L-Thyroxine Treated Hypothyroid Acute Forced Swimming Group (L-Thyroxine ttt HS):**

will receive (PTU) for 3 weeks, then these animals will be submitted to acute forced swimming to measure the MST test once, then these animals will receive L-Thyroxine hormone for 10 days.

Subgroup VIb:**Irisin Treated Hypothyroid Acute Forced Swimming Group (Irisin ttt HS):**

will receive (PTU) 3 weeks, then these animals will be submitted to acute forced swimming to measure the MST test once, then these animals will receive Irisin hormone (IP) at a dose of $10\mu\text{g}/\text{kg}/\text{day}$ for 10 days.

Maximal Swimming Time (MST):

After 3 weeks acclimatization the animals of Subgroup Ib, I Ib, IIIb and VIb were subjected to swimming for 10 min daily for 7 days. The Maximal Swimming Time expressed as (min) was measured by forcing the animals to swim against load (5% of body weight) attached about 2 inches from the end of the tail then the animals were held out of the water when become fatigued.

For all animals, the body weight, body mass index and abdominal circumference were measured one day before (PTU) and at the end of experiment, blood samples were obtained by decapitation (Aktas et al., 2011) from all rats, the separated sera were stored at -80°C and used for measurements of the following: Total Tri-iodothyronine (T3), Total Thyroxine (T4) and Thyroid Stimulating Hormone (TSH) by enzyme-linked immunosorbent-assay (ELISA) from Sigma-Aldrich according to the method described by (Das et al., 2008). Triglycerides level was measured by glycerol-3- phosphate oxidase (GPO) enzymatic method obtained from Biodignostic Company (Fossati and Prencipe, 1982). Cholesterol level by Calorimetric method from BioSystems Company. (Tietz et al., 1976). Low Density Lipoprotein-Cholesterol level by Calorimetric method from BioSystems Company. (Fruchart, 1982). High Density Lipoprotein-Cholesterol level by Calorimetric method from BioSystems Company. (Grove,1979).

Phospholipids level by Calorimetric method from Biodignostic Company. (Yukuo et al., 1980). Irisin level was measured by using (ELISA) kits obtained from Bio Kit Company, Concentrations of the hormone were shown as ng/ml. (Aydin S. et al, 2014). Creatin Kinase (CK) level by Calorimetric method from Egyptian Company for Biotechnology (Tietz, 1999).

The sacrificed animals were packed in a special package according to safety precautions and infection control measures.

Statistical analysis:

Results were expressed as Mean \pm SD and all statistical comparisons were made by means of one-way ANOVA test, followed by Tukey's post hoc analysis, and p values less than 0.05 were considered statistically significant. The analysis was performed by statistical package for the social science software (SPSS version 22.0.).

Results:-

In hypothyroid rats, irisin injection only caused decrease in body weight, abdominal circumference and body mass index with decrease in lipid profile but no improvement in thyroid function tests. While L-thyroxine injection only caused improvement in thyroid function tests but no significant improvement in anthropometric measurements and lipid profile. On the other hand, injection of both irisin and L-thyroxine gave the best results in all parameters as both improved anthropometric measurements, lipid profile and thyroid function tests. It is clear from the results of the present work that hypothyroid animal had significant increase in serum CK levels as compared to normal euthyroid rats. L-thyroxine when given as treatment to hypothyroid rats caused significant reduction in CK. However, when irisin was given as a treatment to hypothyroid animals, it caused more increase in irisin than hypothyroid rats

Acute exercise causes significant decrease in MST in hypothyroid animals and those treated with irisin as compared to control and those of hypothyroid treated with thyroxine. However Acute exercise caused no significant change in all other parameters studied.

Discussion:-

Irisin physiology and its regulation remain largely unknown (Zybek-Kocik et al., 2018). Regulation of irisin under conditions of metabolic derangements as in alter thyroid status as hypothyroidism remain to be investigated. (Yang et al., 2019).

The relationship between irisin and thyroid disorders is thought to be highly complex and multifaceted, It is evident that induction of hypothyroidism causes significant decrease in the level of T3 and T4 with significant increase in TSH in hypothyroid control group compared to normal euthyroid animals. L-thyroxine when given as treatment to hypothyroid rats it caused significant increase in T3 and T4 and significant decrease in TSH. However, when these animals are treated with irisin it caused insignificant change in these parameters when compared with hypothyroid rats denoting that irisin didn't affect these parameters in hypothyroid animals.

Ateş et al., (2016) reported that irisin level and T4 level are independent risk factors for hypothyroidism. When hypothyroid rats are treated with irisin combined with L-thyroxine it caused significant increase in T3 and T4 and significant decrease in TSH, this could be secondly to the effect of L-thyroxine. Results of the present work revealed that in hypothyroid control group, induction of hypothyroid in animals caused significant increase in BW, AC and BMI suggesting that even mild thyroid dysfunction in the form of hypothyroidism is linked to and represents a risk factor for overweight and obesity; (Sanyal and Raychaudhuri, 2016)

The cause of the weight gain in hypothyroid individuals is complex, and not always related to excess fat accumulation. Most of the extra weight gained in hypothyroid individuals may be due to excess accumulation of salt and water. (Liamis et al., 2017). Another cause of weight gain is the presence of insulin resistance in hypothyroidism. Both high BMI and high body fat percentage were strongly related to insulin resistance (Lim et al., 2015). Brent et al., 2011 stated that in hypothyroidism the increase in BW could be due to insulin resistance (Lim et al., 2015) or increase leptin and leptin resistance (Shomon, 2019) or a decrease in tissue sensitivity to leptin (Gruzdeva et al., 2019). Also, could be due to increase in irisin level (Eun et al., 2019)

However, many mechanisms and factors could explain the significant increase of these anthropometric parameters in hypothyroid rats observed in this work in spite of significant increase in irisin endogenously released secondary to hypothyroidism by to 21.5 % increase. However, irisin given exogenously to these rats caused significant decrease which amount to 43.7 % in BW, AC and BMI. Eun et al., (2019) concluded that both irisin treated cells and FNDC5-overexpressed cells resulted in inhibition of adipogenesis. ie the exogenously released irisin has double effect than that released endogenously.

L-thyroxine when given as treatment to hypothyroid rats it caused insignificant change in these anthropometric parameters indicating that L-thyroxin didn't affect these parameters. However, when L-thyroxine combined with irisin caused significant reduction in BW, AC and BMI secondary to the effect of irisin.

It is evident from the results of the present work that irisin level is significantly increased in hypothyroid rats as compared to euthyroid animal.

Studies on irisin level with regard hypothyroidism are controversial. Plasma irisin levels displayed significant increases in the case of hypothyroidism. (Atici et al., 2018). Halpern., (2016) (Ateş, et al., (2016) (Samy et al., 2015) ,On the other hand, Ruchala et al., (2014) concluded that the irisin levels were lower in hypothyroid.The significant increase in serum irisin with hypothyroidism, could be possibly as a response to oxidative damage(Halpern., 2016) and/or myopathy observed in hypothyroidism. (Villanueva et al., 2013) or could be due to increased TSH levels which might cause increased irisin (Ateş et al., 2016).

When L-thyroxin is given to these rats as a treatment the level of irisin return to normal euthyroid level, when irisin is injected in hypothyroid animals, it caused more increase in irisin nearly reaching double values. However, when both L-thyroxin and irisin are injected the level of irisin remained high denoted the injection of irisin mask the lowering effect of L-thyroxin on irisin levels.

It is clear from the results of the present work that hypothyroid animal had significant increase in serum CK levels as compared to normal euthyroid rats. The increased CK activity in hypothyroidism. leads to a hypometabolic state which can cause a reduction in glycolysis and oxidative phosphorylations and thus reducing adenosine triphosphate (ATP) below the normal limit that lead to increase cell permeability and leakage creatine kinase from cell to circulation (Hemavathi et al., 2016). Also CK-MM isoenzyme increased in hypothyroid that lead to increase of C.K activity (Ranka and Mathur., 2003). Decrease in enzyme clearance. may also contribute to increase in serum CK levels. (McGrowder et al., 2011). Another possible cause of the increase CK in hypothyroidism is myopathy, muscle weakness.Koner and Chaudhuri., (2019). Archna et al., (2007) observed that there was increase in CK levels in patients with decreased T3 levels, serum CK level was positively correlated with TSH levels. (Lima et al., 2012), serum CK was negatively correlated with T4 (Hekimsoy and Oktem; 2005).

L-thyroxine when given as treatment to hypothyroid rats caused significant reduction in CK because it caused improvement of all the above factors. (Madhu et al. in 2010). However, when irisin was given as a treatment to hypothyroid animals, it caused more increase in irisin Whether, the increase in irisin levels is a specific and metabolically important effect or whether it is related unspecifically to myocyte damage and/or cellular stress needs to be investigated further (Gouni-Berthold et al., 2013). No significant reduction in the levels of CK was observed in serum collected from irisin injected mice, when compared to controls. Therefore, serum CK levels may not accurately reflect the extent of muscle damage present in irisin injected mice. (Reza et al., 2017). L-thyroxine when combined with irisin caused significant reduction in CK secondly to the effect of L-thyroxine.

Results of the present study denoted that there is dyslipidemia in hypothyroid animals when compared to normal control. These results were in accordance to those previously reported by Asvold et al., (2007) The decreased T3 seen in hypothyroidism may result in increased serum cholesterol (Garduno-Garcia et al., 2010). Insulin resistance may be responsible for this dyslipidemia (ormazabal et al 2018). Also, hypothyroidism is characterized by impairment of redox potential With disturbed lipid metabolism (Babu et al., 2011). Many mechanisms and factors could explain the dyslipidemia in hypothyroid rats in spite of significant increase in irisin level in these animals.

The results of the present work revealed that, irisin when given as treatment to hypothyroid animals cause improvement of dyslipidemia (Oelmann et al., 2016) Bahls and Nele., (2016) also reported that circulating irisin

concentrations are associated with a favorable lipid profile. On the other hand, Shanshan et al (2015) reported that irisin worsens lipid profile.

L-thyroxine when given as treatment to hypothyroid rats, it caused insignificant change in these parameters, when L-thyroxine combined with irisin caused significant improvement of dyslipidemia secondly to the effect of irisin.

Acute exercise causes significant decrease in MST in hypothyroid animals and those treated with irisin as compared to control or those of hypothyroid treated with thyroxine. Razvi et al., (2018) reported that low exercise tolerance were frequently observed in hypothyroidism. but after hormone replacement with L-thyroxine, exercise capacity can be attained back. (Bansal and Sayashree, 2015)

Comparing the levels of irisin after acute forced swimming in hypothyroid rats with those before exercise revealed insignificant change also comparing these levels after acute forced swimming in hypothyroid treated rats with either L-thyroxine or irisin with those before exercise reveal insignificant change.

It can be concluded that there is no definitive link between exercise and irisin released. (Fatouros., 2018). Absence of the increase of irisin in acute forced swimming hypothyroid animal is previously reported by Józkw et al., (2019) Pang et al., (2018)

As regard CK no effect of acute forced swimming in all subgroups and the change in CK is similar to those without exercise,

Result of the present work approved that no effect of acute forced swimming exercise on lipid profile in hypothyroid animal and hypothyroid treated with L-thyroxin or irisin, Similar results are obtained by (Sabbaghian and Gholami ,2010) and (Hernandez-Torres et al., 2009)

Table 1:- Mean and \pm SD of Maximum swimming time (MST min) in all subgroups with exercise in rats.

subgroups	I Euthyroid Control (EC) subgroup	II Hypothyroid Control (HC) Subgroup	III L-Thyroxine ttt Hypothyroid (H) subgroup	VI Irisin ttt Hypothyroid(H) subgroup
MST min				
Mean	14.2	7.1	14.1	7.2
\pm SD	\pm 0.66	\pm 0.71 ^a	\pm 0.69 ^b	\pm 0.72 ^{ac}
F	332.65			

P was considered significant at <0.05 .

a Significance vs EC subgroup

b Significance vs. HC Subgroup

c Significance vs. L-Thyroxine ttt H subgroup

Table 2a:- Significant and % increase between initial and Final change in body weight (BW in gm) Abdominal Circumference (AC in cm) and Body mass index (BMI in gm/c.m²) of male rats without exercise.

subgroups	Without Exercise				
	Euthyroid Control (EC) subgroup	Hypothyroid Control HC subgroup	L-Thyroxine ttt Hypothyroid (H) subgroup	Irisin ttt Hypothyroid (H) subgroup	Irisin & L- Thyroxine ttt Hypothyroid (H) subgroup
parameters					
BW (gm)	6.4%	40%*	29.8%*	5%	2.5%
AC (c.m)	1.8%	26.8%*	25.2%*	5.9%	2.2%
BMI (gm/c.m ²)	7.1%	39.1%*	32%*	6.1%	2.2%

*Denote statistical significance of the final vs initial measurement in all parameters studied $P \leq 0.05$

Table 2b:- Significant % increase between initial and Final change in body weight (BW) Abdominal Circumference (AC) and Body mass index (BMI) of male rats with exercise.

subgroups	With Exercise			
	Euthyroid Control (EC)	Hypothyroid Control HC subgroup	L-Thyroxine ttt Hypothyroid (H) subgroup	Irisin ttt Hypothyroid(H) subgroup

parameters	subgroup			
BW (gm)	4.7%	30.7% *	12.9%	5.2%
AC (c.m)	5.1%	30.1%*	7.0%	3.9%
BMI (gm/c.m ²)	13%	30.4%*	32.6%	4.3%

*Denote statistical significance of the final vs initial measurement in all parameters studied $P \leq 0.05$

Table 3a:- Mean and \pm SD of Serum T3, T4, TSH, irisin, CK in male rats without exercise.

subgroups	Without exercise				
	Euthyroid Control (EC) subgroup	Hypothyroid Control HC subgroup	L-Thyroxine ttt Hypothyroid (H) subgroup	Irisin ttt Hypothyroid (H) subgroup	Irisin & L-Thyroxine ttt Hypothyroid (H) subgroup
Serum T3 (pg/ml)	2.66 ± 0.392	0.25 ^a ± 0.064	2.98 ^b ± 0.438	0.22 ^{ac} ± 0.053	2.79 ^{bd} ± 0.467
Serum T4 (ng/dl)	2.19 ± 0.205	0.21 ^a ± 0.022	2.31 ^b ± 0.132	0.23 ^{ac} ± 0.029	2.33 ^{bd} ± 0.092
Serum TSH (uIU/ml)	1.50 ± 0.039	2.64 ^a ± 0.066	1.53 ^b ± 0.037	2.63 ^{ac} ± 0.034	1.51 ^{bd} ± 0.045
Serum irisin (ng/ml)	30.54 ± 2.29	38.84 ^a ± 1.65	29.79 ^b ± 1.62	69.09 ^{a,bc} ± 2.63	70.69 ^{a,bc} ± 2.76
Serum CK (U/L)	165.65 ± 5.33	400.68 ^a ± 6.33	167.13 ^b ± 3.92	402.28 ^{ac} ± 7.17	169.02 ^{bd} ± 3.04

P was considered significant at <0.05 .

b Significance vs. HC Subgroup

d Significance vs Irisin ttt H subgroup

a Significance vs EC subgroup

c Significance vs. L-Thyroxine ttt H subgroup

Table 3b:- Mean and \pm SD of Serum T3 ,T4 ,TSH, irisin ,CK in male rats with exercise.

subgroups	With Exercise			
	Euthyroid Control (EC) subgroup	Hypothyroid Control HC subgroup	L-Thyroxine ttt Hypothyroid (H) subgroup	Irisin ttt Hypothyroid(H) subgroup
Serum T3 (pg/ml)	2.74 ± 0.332	0.24 ^a ± 0.068	2.82 ^b ± 0.456	0.23 ^{ac} ± 0.051
Serum T4 (ng/dl)	2.24 ± 0.177	0.22 ^a ± 0.027	2.34 ^b ± 0.109	0.23 ^{ac} ± 0.026
Serum TSH (uIU/ml)	1.49 ± 0.034	2.62 ^a ± 0.038	1.51 ^b ± 0.027	2.67 ^{ac} ± 0.026
Serum irisin (ng/ml)	32.70 ± 3.61	41.09 ^a ± 1.76	31.59 ^b ± 1.74	70.58 ^{abc} ± 1.93
Serum CK (U/L)	168.58 ± 4.52	405.42 ^a ± 5.57	169.92 ^b ± 3.62	408.09 ^{ac} ± 5.93

P was considered significant at <0.05 .

b Significance vs. HC Subgroup

d Significance vs Irisin ttt H subgroup

a Significance vs EC subgroup

c Significance vs. L-Thyroxine ttt H subgroup

Table 4a:- Mean and \pm SD of Serum Triglycerides, Cholesterol, LDL-Cholesterol, HDL-Cholesterol Phospholipids in male rats without exercise.

subgroups	Without exercise				
	Euthyroid Control (EC) subgroup	Hypothyroid Control HC subgroup	L-Thyroxine ttt Hypothyroid (H) subgroup	Irisin ttt Hypothyroid (H) subgroup	Irisin & L-Thyroxine ttt Hypothyroid (H) subgroup

Serum Triglycerides (mg/dl)	137.31 ±9.01	187.17 ^a ±8.73	177.54 ^a ±8.66	148.34 ^{bc} ±9.87	175.93 ^{bc} ±7.52
Serum Cholesterol (mg/dl)	118.53 ±4.88	173.92 ^a ±4.25	169.69 ^a ±3.23	112.97 ^{bc} ±4.33	168.58 ^{bc} ±3.09
Serum LDL-Cholesterol (mg/dl)	47.23 ±4.86	92.87 ^a ±8.04	84.96 ^a ±4.53	48.64 ^{bc} ±5.19	85.55 ^{bc} ±5.98
Serum HDL-Cholesterol (mg/dl)	36.21 ±3.43	21.44 ^a ±2.89	24.91 ^a ±2.43	35.41 ^{bc} ±3.34	26.64 ^{bc} ±2.83
Serum Phospholipids (mg/dl)	68.2 ±2.87	115.8 ^a ±3.02	111.0 ^a ±6.46	68.5 ^{bc} ±3.31	110.8 ^{bc} ±5.61

P was considered significant at <0.05.

a Significance vs EC subgroup

b Significance vs. HC Subgroup

c Significance vs. L-Thyroxine ttt H subgroup

d Significance vs Irisin ttt H subgroup

Table 4b:- Mean and ± SD of Serum Triglycerides, Cholesterol, LDL-Cholesterol, HDL-Cholesterol Phospholipids in male rats with exercise.

subgroups parameters	With Exercise			
	Euthyroid Control (EC) subgroup	Hypothyroid Control HC subgroup	L-Thyroxine ttt Hypothyroid (H) subgroup	Irisin ttt Hypothyroid(H) subgroup
Serum Triglycerides (mg/dl)	138.95 ±8.49	181.43 ^a ±8.25	175.93 ^a ±7.52	148.73 ^{bc} ±8.36
Serum Cholesterol (mg/dl)	117.09 ±5.52	169.50 ^a ±4.31	168.58 ^a ±3.09	118.40 ^{bc} ±4.12
Serum LDL-Cholesterol (mg/dl)	45.51 ±5.99	90.43 ^a ±8.38	85.55 ^a ±5.98	52.48 ^{bc} ±5.09
Serum HDL-Cholesterol (mg/dl)	39.35 ±3.59	21.46 ^a ±2.37	26.64 ^a ±2.83	37.34 ^{bc} ±2.76
Serum Phospholipids (mg/dl)	66.9 ±2.53	113.9 ^a ±2.73	110.8 ^a ±5.61	70.9 ^{bc} ±3.69

P was considered significant at <0.05.

a Significance vs EC subgroup

b Significance vs. HC Subgroup

c Significance vs. L-Thyroxine ttt H subgroup

d Significance vs Irisin ttt H subgroup

Conclusion:-

We conclude that irisin has a major role in reducing weight by converting white fat tissue into brown adipose tissue and then to heat. On the other side of the study, irisin has no direct effect on improving the secretion of thyroid hormones in people with thyroid hormone deficiency. Also, the injectable exogenous irisin has a better and more potent effect than the endogenous irisin resulting from acute short-term exercise.

Recommendations:-

We should take more attention from the success results of injectable irisin in reducing weight to make trials for injection of local irisin hormone in adipose tissue as a safe alternative for surgical operations. Also, in regard to hypothyroidism, Creatine Kinase may be used as a marker to determine its degree. Finally, it will be more fair in the future to compare injectable exogenous irisin with chronic exercise at constant period.

Disclaimer:

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