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RESEARCH ARTICLE

PHYSICAL EXERCISE INDUCES IRISIN LEVELS ASSOCIATED WITH IMPROVED COGNITIVE FUNCTIONS AND GLUCOSE TOLERANCE IN OBESE AND NORMAL WEIGHT EGYPTIAN SUBJECTS: A 3-MONTH INTERVENTIONAL STUDY.

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Abstract

Introduction: Cognitive impairment and glucose intolerance are prevalent in obese subjects. Irisin, a recently identified modifier of cognitive functions and glucose metabolism, was reported to be induced by physical exercise. We examined the association of exercise-induced irisin levels with improved cognitive functions and glucose metabolism in both obese and normal weight subjects.

Subjects and Methods: 120 subjects, both males and females, comprised of 60 obese and 60 normal-weight subjects were undergone supervised active aerobic exercises for 3-months. Irisin levels, cognitive functions, fasting blood glucose, insulin, homeostatic model assessment of insulin resistance index (HOMA-IR) were assessed at the initiation and termination of the study.

Results: Obese subjects demonstrated lower irisin levels, impaired cognitive functions and higher insulin as well as HOMA-IR levels compared to the normal weight group. Physical exercise induced significant upregulation of irisin levels together with improvement of cognitive functions and significant reduction of insulin and HOMA-IR levels in both groups. Exercise-induced irisin levels demonstrated significant positive correlations with improved cognitive functions and significant negative correlation with insulin level and HOMA-IR.

Conclusion: Physical exercise improves cognitive functions and glucose metabolism. Our results suggest that irisin could be an important molecular mediator and therapeutic target for improving cognitive functions and glucose metabolism.

Introduction:-

Obesity constitutes a worldwide problem associated with a wide range of health-related disorders including cognitive impairment, insulin resistance, diabetes, and others.[1, 2] Obesity-associated cognitive impairment was

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shown to span several domains including memory, attention, and executive functions.[1] Several mechanisms were proposed to explain obesity-associated disorders including vascular and inflammatory pathogenesis. [3, 4]

Irisin, a recently identified myokine, was proposed to have beneficial effect on obesity, cognitive functions and glucose metabolism.[5]Irisin is released into the circulation from the cleavage of fibronectin type III domain containing5 (FNDC5) regulated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). [5, 6] In the brain, irisin was found to be expressed in the hippocampus, cerebellum, olfactory bulb, pons, and midbrain.[7]Irisin was shown to induce the expression of brain derived neurotrophic factor (BDNF) and other neuroprotective genes.[8] BDNF is important for synaptic plasticity and hippocampal function involved in learning and memory.[9] The role of irisin in regulating glucose metabolism has been recently discovered. Irisin improved glucose tolerance, reduced fasting insulin, and protects diet-induced obesity and diabetes in mouse models.[5, 10] Moreover, irisin appears to play a role in converting white adipose tissue to brown adipose tissue which correlates with improvements in glucose tolerance in obese mice.[11]

The role of physical exercise on managing obesity is well documented. Further, several studies have shown that aerobic exercise could have beneficial effects on cognitive functions and glucose metabolism.[12, 13] Recently, physical exercise was reported to induce irisin release both from skeletal muscles and hippocampus.[14, 15] Therefore, irisin was proposed as an important pathway involved in mediating exercise-induced benefits on body weight, diabetes, metabolic, and cognitive functions .[5] Previous studies focused largely on the effects of medium to long term (>6-months) exercise training on cognitive functions.[16, 17] However, the effect of short term physical exercise was not verified. The objective of this study was formulated to assess the effect of 3-months aerobic exercise on irisin levels and its association with changes in some cognitive functions in obese and normal-weight subjects. In addition, we explored a possible association between irisin levels and some glucose metabolic parameters.

Subjects and Methods:-

Subjects:-

This study was conducted in the period from January 2017- May 2017. The study comprised 2 groups; an obese group (60 subjects with BMI ≥ 30 kg/m2) and a normal weight group (60 subjects with BMI < 25 kg/m2).[18] The obese group was randomly selected from the attendants of Obesity Management and Research Unit, Faculty of Medicine, Zagazig University, whereas the normal-weight control group was randomly selected from the attendants of Physical Education Training Program, Zagazig University. Obese subjects were not allowed to follow a weight-loss diet-regimen during the study. Consent was obtained from all participants.

Inclusion criteria: Any subject aged from 18 - 50 years.

Exclusion criteria: 1) Current medical illness or neurological condition that might affect cognitive functions or for which exercise is contraindicated 2) History of head trauma with loss of consciousness for more than 2 minutes 3) Illiterate or having learning disability 4) Moderate or severe depression according to Beck depression Inventory[19] 5) Use of psycho-active medications.

Ethical consideration: Participants were informed about the research procedures and gave informed consent in writing. The study was done according to the rules of the Local Ethics Committee of Faculty of Medicine, Zagazig University, Egypt.

Methods:-

Aerobic Exercise training program:-

All participants attended supervised aerobic training program, three sessions/ week for three months. Every session lasted for 60 minutes. The aerobic training program was started on the electronic treadmill (luxurious one-way treadmill 901, Chinese) with a 5-minute warm-up period performed at a low load. Then active phase in the form of walking/running gradually increased from 20 to 30 minutes, and its intensity being increased gradually from 60% to 70% of the maximum HR (HR max) achieved in a reference, which was performed in accordance with a modified Bruce protocol. This rate was defined as the training HR (THR). The session ended with a 5-minute recovery and relaxation phase.[20]

Anthrompetric measurements: For all participants before and after exercise program, body weight was measured in light clothing with electronic scales to 0.1 kg precision (Seca, Hamburg, and Germany). Height was measured in a

standing position without shoes with fixed stadiometer (Seca). BMI was calculated by dividing body weight in kilograms by height in meters squared. Waist circumference (WC) was measured with a non-stretchable tape at the midpoint between the lower rib margin and the iliac crest with the subject standing at the end of normal expiration.[21]

Neurocognitive assessment: Participants in both groups of the current study completed a battery of neurocognitive tests which focused on memory, attention, and executive function assessment. The cognitive evaluation was done twice: baseline assessment was conducted at the start of the study and the second evaluation was conducted after completing the three months aerobic training program. All neurocognitive testes were done in a face–to-face interview at morning in a quiet room with five minutes break after each test.

Logical memory subtest of the Wechsler adult intelligence scale [22] **:** We used the logical memory subtest of the Wechsler scale which is a validated scale for memory assessment in adult. A short story of 25 items was introduced to the participants and they asked to repeat it immediately and after 30 minutes. The total score is the number of remembered items in the story with a maximum score = 25.

Trail making B test: This test was used to assess the executive functions. It depends on mental flexibility, good attention, rapid performance and visual- motor coordination. Subjects were asked to draw successive lines between numbers and letters: numbers from 1 through 13 and letters A through L. Score is the total time in seconds to complete the test.[23]

Digit span test of the Wechsler adult intelligence Scale [22] **:**
Digit span tests were used to evaluate attention (forward test), divided attention and central executive functions (backward test). Subjects were asked to recall a list of numbers over 2 trials. On the first trial, numbers are recalled in the same order of presentation (forward), and in the second trial numbers are recalled in reverse order (backward).

Digit symbol test:
This test requires good attention, psychomotor speed processing and visual-motor coordination. Subjects are given a code table displaying the correspondence between pairs of digits (from 1 to 9) and symbols. They were asked to draw the corresponding symbol under each digit presented in the table. The score of this test is the numbers of the correct symbols copied within a 90-seconds time limit. [24]

Blood sampling:-
Fasting (12h) blood samples were taken at the beginning of study after estimation of cognitive performance. Termination fasting (12h) blood samples were taken 48 h after the last training session. Five ml of blood sample was collected by standard venipuncture, left to clot for 1 hour, then serum were separated by centrifugation at 3000 rpm for 15 min. Serum samples were stored at - 80 ℃ until biochemical analysis.

Biochemical Analysis: Serum is analyzed for irisin levels using enzyme-linked immunosorbent assay (ELISA) kit (Catalog no: EK-067-52, Phoenix Pharmaceuticals Inc., CA, USA), for glucose level using glucose enzymatic-liquizyme kits (Biotechnology, Egypt), for insulin level using KAP1251-INS-EASIA Kits (BioSource Europe S.A., Belgium). HOMA-IR was calculated based on serum insulin according to the formula described by **Matthews et al.**[25] as HOMA- IR = fasting serum glucose (mg/dl) x fasting serum insulin (μIU/ml) /405.

Sample size: Physical activity was reported to be associated with higher irisin levels in obese subjects compared to the healthy controls[26] with an estimated effect size of 0.77. To detect this effect size when evaluating the effect of physical exercise on irisin levels in obese and normal weight control, a sample size of 55 subjects in each group is needed at achieve 95% power at 5% alpha level of significance. We recruited 60 subjects per group. Sample size was calculated using G*Power software package (version 3.1.9.2, Franz Faul, Germany).

Statistical Analysis:-
Statistical analysis was performed using SPSS v. 20.0 for Windows (SPSS Inc., Chicago, IL, USA). [27] Continuous variables were presented as mean ± SD. Normality distribution was checked with Shapiro–Wilk test. Wilcoxon-signed rank test was used to examine the effect of exercise (comparing post- and pre-exercise levels) within each group. Partial correlation was used to assess the association between exercise-induced changes in irisin levels and changes in cognitive and glucose metabolic parameters. Adjustment of partial correlation was performed by controlling for all confounding variables (age, gender, years of education, duration of obesity in obese subjects),

other explanatory variables (changes in glucose, insulin, HOMA-IR, BMI, WC), together with the initial (pre-exercise) level of the studied variable (to control for heterogeneity of the initial levels among subjects). Mann-Whitney U Test was used to compare the adjusted mean changes induced by exercise in obese and normal-weight groups. Adjusted exercise-induced changes were estimated using multiple linear regression with all confounding, possible explanatory variables, and the initial level of the dependent variable (to control for heterogeneity of the initial levels among subjects) as independent variables. The statistical significance was set at $P \leq 0.05$.

Results:-

Comparison of basal characteristics in obese and normal-weight groups.Table (1) shows comparison of basal (before exercise) characteristics in both obese and normal-weight groups. There was no significant difference in the mean ages of both groups (32.34±5.95 versus 32.23±6.15). Also, there was no significant difference in the years of education (12.53±3.16 and 11.95±3.6) and MMSE scores (29.3±1.02 and 29.1±1.1) between control and obese groups respectively. Regarding BMI, WC, insulin levels and HOMA-IR there was a significant increase in those parameters (**P<0.001)** between obese and control while there was a significant decrease in irisin levels in obese group compared to controls (**P<0.001)**. Also, obese subjects gained lower scores in most of the neurocognitive tests as compared to the controls (**P<0.001**).

Physical exercise induces irisin levels, enhance cognitive functions, and improve metabolic profile in obese and normal-weight groups. Table (2) showed thatboth groups (obese and controls) gained a better post exercise performance in neurocognitive tests in comparison to their baseline scores. **Table (3)** showed a significant elevation of irisin levels in both control and obese groups **(P<0.01, P<0.001** respectively**)** with significant reduction in insulin levels **(P<0.001**, **P<0.001)** and HOMA-IR **(P<0.05**, **P<0.001)** in control versus obese respectively in comparison to their baseline assessment, however there were a non-significant post exercise reduction of BMI and WC (P>0.05).

Association of exercise-induced irisin changes with cognitive and metabolic changes. We used multiple regression analysis with irisn change as the dependent variable and confounding variables (age, gender, years of education, duration of obesity in obese subjects), other changes in the levels of (glucose, insulin, HOMA-IR, BMI, WC), and the initial level of the dependent variable (before exercise) to assess partial correlation between irisin changes and the variable of interest. **Table 4**, shows partial correlation between exercise-induced irisin changes and other variables changes in both obese and normal weight groups. Figure 1, Shows that exercise-induced irisin changes demonstrated significant positive correlation with the changes of Immediate memory, Delayed memory, Digit Symbol, Digit Span Forward, Digit Span Backward and negatively correlated with Trail Making B test. Conversely, figure 2 shows that irisin changes demonstrated significant negative correlation with insulin level and HOMA-IR.

Comparison of exercise-induced mean changes in obese and normal weight groups. We used the mean adjusted changes to compare exercise-induced changes of irisin, cognitive, and metabolic levels in obese and normal weight groups. The adjusted mean changes were determined using the mean predicted changes determined from multiple regression with the variable of interest as the dependent variable and controlling for the effect of confounding variables (age, gender, years of education, duration of obesity in obese subjects), other variable changes, and the initial level of the dependent variable (before exercise). Fig. 3 shows significant difference as regard irisn level, Delayed memory , Digit Span Forward and Digit Span Backward . Fig. 4 shows significant difference as regard Insulin and HOMA-IR.

Table 1:- Comparison between the obese and normal-weight groups regarding baseline neurocognitive assessment, anthropometric and laboratory parameters.

Variables	Normal weight Control N=60	Obese N=60	p-value
Immediate Memory	18.02±2.48	15.95±2.18	P < 0.001**
Delayed Memory	13.35±1.77	11.95±1.54	P < 0.001**
Trail making B test	90.00±11.49	102.22±9.71	P < 0.001**
Digit Symbol test	57.17±5.05	52.80±4.62	P < 0.001**
Digit Span Forward	7.38±1.35	6.67±1.61	P < 0.05*
Digit Span Backward	5.88±0.80	5.07±1.22	P < 0.001**
BMI (kg/m^2)	23.22±1.52	38.01±3.63	P < 0.001**

WC (Cm)	75.87±6.56	102.33±8.13	P < 0.001**
Glucose (mg/dl)	80.03±6.48	84.55±11.21	P > 0.05
Insulin (µIU/ml)	6.36±1.84	18.32±5.80	P < 0.001**
HOMA-IR	1.26±0.38	3.94±1.62	P < 0.001**
Irisin (ng/ml)	86.56±11.82	65.39±15.79	P < 0.001 **

BMI: body mass index, **WC:** waist circumference, **HOMA-IR:** homeostatic model assessment of insulin resistance index, *****Significant ($p \leq 0.05$), ****** Highly Significant ($p < 0.001$)

Table 2:-Comparison of the effect of exercise on cognitive functions within each group (post- and pre-exercise).

Variables	**Normal weight control**		**Obese**	
	Baseline N=60	**Post-exercise N=60**	**Baseline N=60**	**Post-exercise N=60**
Immediate Memory	18.02±2.48	20.78±3.02	15.95±2.18	18.80 ±3.66
	P<0.001**		P<0.001**	
Delayed Memory	13.35±1.77	14.62±2..06	11.95±1.54	14.65±2.22
	P<0.001**		P<0.001**	
Trail making B	90.00±11.49	83.65±12.81	102.22±9.71	95.10±10.69
	P<0.001**		P<0.001**	
Digit Symbol	57.17±5.05	63.28±8.48	52.80±4.62	58.18±7.89
	P<0.001**		P<0.001**	
Digit Span Forward	7.38±1.35	7.93±1.31	6.67±1.61	8.60±2.63
	P<0.01**		P<0.001**	
Digit Span Backward	5.88±0.80	6.68±1.30	5.07±1.22	6.57±1.69
	P<0.001**		P<0.001**	

*****Significant ($p \leq 0.05$), ****** Highly Significant ($p < 0.001$)

Table 3:- Comparison of the effect of exercise on metabolic function within each group (post- and pre-exercise).

Variables	**Normal weight control**		**Obese**	
	Baseline N=60	**Post-exercise N=60**	**Baseline N=60**	**Post-exercise N=60**
BMI(kg/m^2)	23.22±1.52	23.11±1.45	38.01±3.63	37.99±3.58
	P>0.05		P>0.05	
WC(cm)	75.87±6.56	75.33±6.38	102.33±8.13	101.75±7.16
	P>0.05		P>0.05	
Glucose(mg/dl)	80.03±6.48	78.90±5.89	84.55±11.21	83.45±10.64
	P>0.05		P>0.05	
insulin(µIU/ml)	6.36±1.84	5.58±1.62	18.32±5.80	13.62±6.39
	P<0.001**		P<0.001 **	
HOMA-IR	1.26±0.38	1.15±0.56	3.94±1.62	2.95±1.49
	P<0.05*		P<0.001 **	
Irisin (ng/ml)	86.56±11.82	88.20±10.83	65.39±15.79	74.38±14.38
	P<0.01*		P<0.001**	

BMI: body mass index, **WC:** waist circumference, **HOMA-IR:** homeostatic model assessment of insulin resistance index, *****Significant ($p \leq 0.05$), ****** Highly Significant ($p < 0.001$)

Table4:-Partial correlation of exercise-induced irisin change with observed changes in cognitive and metabolic functions.

Variables	**Normal weight control**		**Obese**	
	r	**P**	**r**	**P**
Immediate Memory	0.729	0.000**	0.422	0.002*
Delayed Memory	0.573	0.000**	0.451	0.001*
Trail making B	-0.644	0.000**	-0.552	0.000**.
Digit Symbol	0.581	0.000**	0.612	0.000**
Digit Span Forward	0.339	0.01*	0.57	0.000**

Digit Span Backward	0.374	0.007*	0.4	0.004*
BMI(kg/m^2)	-0.239	0.088	-0.119	0.404
WC (Cm)	-0.072	0.612	-0.073	0.611
Insulin(µIU/ml)	-0.441	0.001*	-0.516	0.000**
HOMA-IR	-0.392	0.004*	-0.465	0.001*
Glucose	0.209	0.137	0.149	0.295

BMI: body mass index, **WC:** waist circumference, **HOMA-IR:** homeostatic model assessment of insulin resistance index, *****Significant ($p \leq 0.05$), ****** Highly Significant ($p < 0.001$)

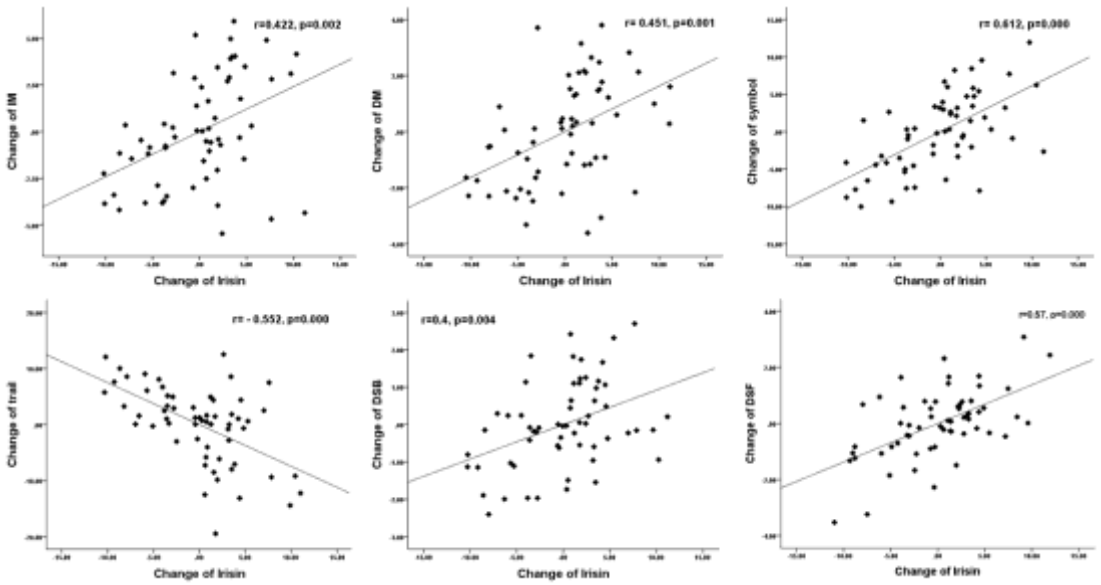


Fig 1:-Partial **c**orrelation between exercise-induced irisn changes and changes in cognitive functions in obese subjects. Partial correlation wasadjusted for all other variables (age, gender, years of education, duration of obesity in obese subjects, and changes in glucose,insulin, HOMA-IR, BMI, WC) and the initial level (before exercise) of the dependent variable using multiple linear regression. **IM**: Immediate memory; **DM**: Delayed memory; **DSF**: Digit span forward; **DSB**: Digit span backward.

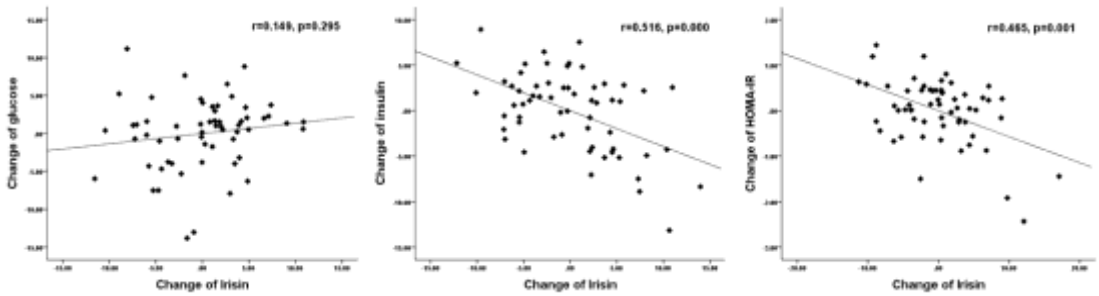
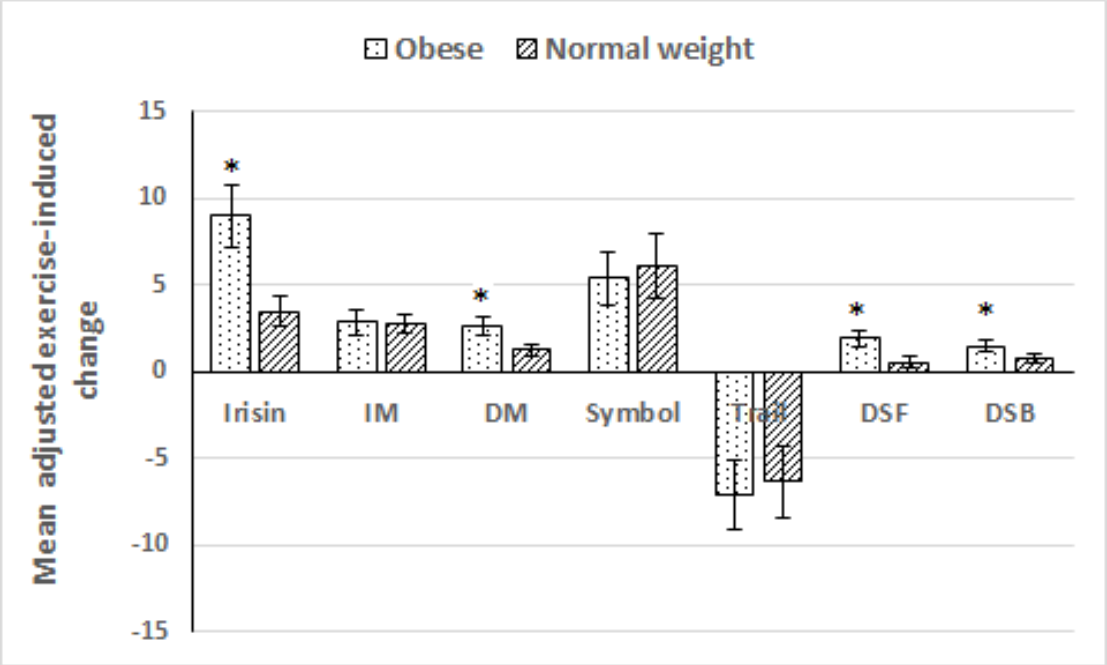
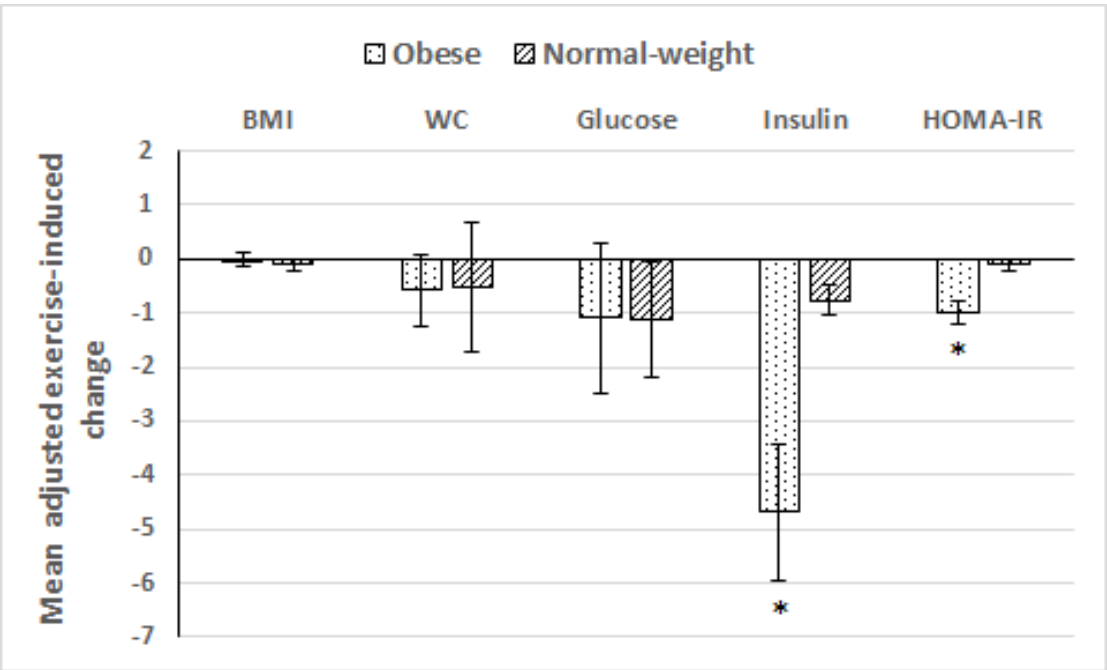


Fig 2:-Partial correlation between exercise-induced irisn changes and changes in metabolic profile in obese subjects. Partial correlation wasadjusted for confounding variables (age, gender, years of education, duration of obesity in obese subjects, and changes in glucose, insulin, HOMA-IR, BMI, WC) and the initial level (before exercise) of the dependent variable using multiple linear regression.



*Significantly higher than normal weight group

Fig 3:- Comparison of exercise-induced mean changes in irisin levels and cognitive functions. Mean changes were adjusted for the changes in all other variables (age, gender, years of education, duration of obesity in obese subjects, and changes in glucose, insulin, HOMA-IR, BMI, WC) and initial level of dependent variable using multiple linear regression. **IM**: Immediate memory; **DM**: Delayed memory; **DSF**: Digit span forward; **DSB**: Digit span backward



*Significantly lower than normal weight group

Fig 4:- Comparison of exercise-induced mean changes in metabolic functions, BMI, WC. Mean changes were adjusted for the changes in all other variables (age, gender, duration of obesity in obese subjects, and changes in glucose, insulin, HOMA-IR, BMI, WC) and initial level of dependent variable using multiple regression.

Discussion:-

Obesity is known to be associated with deteriorated cognitive function and glucose metabolic regulation. We observed that obese group had multiple cognitive deficits compared to normal weight group. Using the logical memory recall subtest of Wechsler adult intelligence scale to assess verbal memory, obese group demonstrated lower scores in both immediate and delayed memory. Our results were consistent with previous studies reported a significant difference in memory performance between obese and non-obese individuals.[28, 29] Executive functions are a collective term used to describe a complex set of cognitive processes necessary for responding adaptively in different situations. It includes a variety of higher order tasks including problem solving, planning and judgment and decision making.[30] Our results demonstrated significant decline in executive functions in obese subjects as evidenced by significantly higher scores in trail making B test compared to the normal weight controls. This was in agreement with previous studies demonstrated that executive functions, especially decision making [26, 31, 32], cognitive flexibility, as well as inhibition response[1], were impaired in obese subjects. Psychomotor performance is considered the coordination of a sensory or cognitive activity and motor performance.[30]Obese subjects in our study demonstrated significantly lower scores on the digit symbol test suggesting deteriorated psychomotor performance. **Cournot et al.**[28] and **Etou et al.**[33] reported the same finding, which lend support to our results.

Aerobic exercise was shown to have beneficial effects on different cognitive functions [34, 35]. Recently, FNDC5/irisin was proposed as an important pathway mediating exercise-associated improved cognitive functions. Physical exercise stimulates the FNDC5/irisin mRNA expression both centrally in the hippocampus and peripherally in the skeletal muscles in a PGC-1α-dependent manner. In the brain, FNDC5/irisin expression was demonstrated to increase the expression of brain-derived neurogenic growth factor BDNF.[36] BDNF synthesis and secretion in the hippocampus promotes brain development including neuronal cell survival, differentiation, migration, dendritic arborization, synaptogenesis and plasticity[9]leading to regulation of hippocampal learning and memory.[37]

One goal of the present study was to evaluate the effect of short-term exercise on cognitive functions in obese and normal weight subject. Another goal was to explore if exercise-induced cognitive changes could be correlated with exercise-induced irisin level. Our results demonstrated that practicing aerobic exercise for 3-months significantly improved cognitive performance in both controls and obese groups. These results were in accordance with **Pereira et al.**[38]who concluded that a short course of aerobic training for three months resulted in improved memory performance on the Rey auditory verbal learning test in healthy adults. The obese subjects in our sample demonstrated lower initial (before initiation of the exercise program) irisin levels compared to the normal weight subjects. Low irisin levels in obese subjects were observed in some epidemiological[39, 40] and experimental studies.[41, 42] **Lichtenbelt et al.**[43] observed that the amount of brown adipose tissue was significantly reduced in association with obesity which could reflect lower irisin levels. Adopting aerobic exercise for 3-months significantly induced irisin levels in both control and obese groups. Our results corroborated with those of **Boström et al.**[5] and **Bluher et al.**[44] who reported increased irisin levels after 10 weeks and 1 year of physical exercise, respectively. The exercise-induced irisin levels in our studies were significantly correlated with improved cognitive functions after controlling for confounding factors that could affect cognitive process. Specifically, irisin changes was positively correlated with immediate, delayed logical memory recall test, digit symbol test, and digit span forward and backward but negatively correlated with trail making scores in both control and obese groups. This results support the proposal that irisin is a mediator for improved cognitive functions induced by physical exercise. Our results demonstrated that obese subjects were more responsive to physical exercise in terms of irisin induction and cognitive enhancement. This could be explained by our earlier observation of lower irisin levels and deteriorated cognitive functions in obese group compared to the normal weight group.

Obesity is well known to be associated with disturbed glucose metabolic regulation characterized by glucose intolerance, higher than normal insulin levels, and HOMA-IR[45]. Therefore, a third goal of our study was to evaluate the effect of short-term exercise on glucose metabolic regulation in obese and normal weight subjects and to explore if those effects were correlated with exercise-induced irisin level. Our results demonstrated that 3-months of aerobic exercise were associated with improved glucose tolerance as demonstrated by significant reduction of insulin levels and HOMA-IR in both obese and control subjects. Reduction of insulin and HOMA-IR was not concomitant with increased glucose levels suggesting improved glucose uptake and metabolism. Our results are supported by previous studies, which suggested that aerobic training produces beneficial improvements in glucose tolerance and insulin sensitivity in obese individuals when performed at moderate intensities.[13]We observed significant negative correlation between irisin levels and insulin and HOMA-IR levels**,** which suggest a putative role of irisin in

improving glucose tolerance. Partial support of this role of irisin come from experimental animal models, in which systemic irisin administration was found to improve insulin resistance and enhances lipolysis in obese rats.[46, 47]

One limitation of our study is that it could only provide a proof of association, and not causation, between exercise-induced irisin levels and the observed improved cognitive and glucose tolerance parameters. Although the reported correlations in our study were adjusted by controlling for many confounding and potentially explanatory variables, yet physical exercise could improve cognitive performance and glucose regulation by other mechanisms. Causal association could better be inferred from clinical trials in which irisin is systemically administered into subjects, in the absence of physical exercise, and subsequent changes of cognitive and glucose tolerance parameters could be assessed. Such study design would also be important to study the kinetics of irisn and whether it could cross blood-brain barrier in humans. This would be critical to delineate the role of peripherally- and centrally (brain)-produced irisin in improving cognitive and glucose tolerance, which could lay the basis of a potential therapeutic utilization of irisin.

Conclusion:-

Our study revealed that short-term physical exercise could improve cognitive performance and glucose tolerance in both obese and normal weight subjects of both sex. The observed significant correlation of irisin with exercise-induced changes suggests that irisin could be the mediator of exercise effect. Further research is needed to assess the utility of irisn as a therapeutic target for enhancing cognitive functions and glucose metabolism in different clinical settings.

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