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RESEARCH ARTICLE

INTERVENTION PROGRAM FOR IMPROVING INSULIN SENSITIVITY AND AMELIORATING ADIPOKINES ALTERED SERUM LEVELS IN OBESE AND TYPE-2 DIABETIC CHILDREN.

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Abstract

Objectives: To evaluate therapeutic yield of lifestyle intervention program on body mass index (BMI), insulin resistance (IR) and estimated laboratory markers in obese and diabetic children.

Patients & Methods: Thirty-five obese non-diabetic, 35 type-II diabetic and 20 control children and adolescents were studied. Study children underwent 12-weeks intervention consisted of dieting regimen, aerobic exercise with curcumin as herbal therapy. Serum insulin, progranulin (PGRN), tumor necrosis factor-α (TNF-α), adiponectin and YKL-40 levels were ELISA estimated. Insulin resistance was measured by homeostasis model assessment (HOMA-IR). BMI and HOMA-IR score and laboratory parameters were determined at start and end of the intervention.

Results: At end of intervention, BMI and HOMA-IR variables and score were significantly decreased compared to baseline measures. Baseline serum levels of PGRN, YKL-40 and TNF-α were significantly higher, but adiponectin levels were significantly lower in patients than controls and in diabetics than obese children. At end of intervention, serum PGRN and YKL-40 levels were significantly decreased than baseline levels with significantly higher levels in diabetics than obese. Despite of decreased serum TNF-α levels compared to baseline levels, it was still significantly higher in patients than controls and in diabetics than obese children. Serum adiponectin levels increased but were significantly lower in diabetics and non-significantly lower in obese compared to control levels with significantly higher levels in obese compared to diabetics.

Conclusion: This intervention program allowed reduction of BW and IR and could ameliorate disturbance of adipokines serum levels in obese and diabetic children.

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Introduction:-

Obesity includes a subset of individuals that can be classified as having metabolically healthy obesity. Lower levels of abdominal obesity and insulin resistance are the most consistent predictors of prevalent metabolically healthy obesity status (Heinzle et al., 2015). Rapid infant weight gain is associated with increases in visceral adipose tissue and abdominal subcutaneous adipose tissue, as well as total adiposity and the risk of obesity in middle adulthood (Demerath et al., 2009).

Inflammation process may underlie the development and maintenance of diverse chronic diseases, including diabetes and atherosclerosis. Diabetes can in turn increase the risk of cardiovascular events which can be considered as the most important cause of death in diabetic population (Freitas Lima et al., 2015).

Obesity-induced inflammation acts as a reflex to altered metabolic homeostasis secondary to nutrient overload on the metabolic cells. It involves up-regulation of the genes encoding for cytokines, chemokines and other inflammatory mediators through activated transcription factors (Debnath et al., 2015).

White adipose tissue was recognized as an endocrine organ and an important source of biologically active substances with local and/or systemic action called adipokines (Adamczak and Wiecek, 2013). Increased adipocyte number and adipose-tissue mass have been found to result in increased plasma adipocytokine level except adiponectin, whose plasma concentration is actually low in obesity (Hajer et al., 2008). Inappropriate secretion of several adipokines by the excessive amount of white adipose tissue participates in induction and progress of obesity-related complications (Adamczak and Wiecek, 2013).

Circulating progranulin (PGRN) levels are elevated in patients with type 2 diabetes (T2DM) (Tolkatchev et al., 2008). Increased plasma PGRN levels are associated with impaired glucose tolerance rather than impaired fasting glucose (Sleegers et al., 2010). Tumor necrosis factor-α (TNF-α), besides its proinflammatory property, high TNF-α levels inhibits insulin transduction mechanism, thus leading to inadequate glucose metabolism, insulin resistance (IR) and obesity (Swaroop et al., 2012). Because visceral fat is a source of TNF-α, obesity leads to increased production of this cytokine, which aggravates obesity and a vicious cycle is established leading to predisposition, onset and progression of T2DM along with IR (Bastard et al., 2006). Circulating concentrations of the proinflammatory chitenase-like protein, YKL-40, were significantly higher in obese normoglycemic and T2DM patients compared to lean volunteers (Catalán et al., 2011) and a role of serum YKL-40 was suggested in obesity-related low grade inflammation (Thomsen et al., 2015). Recently, in 2016, increasing body mass index (BMI) in adult offspring born to women with diabetes during pregnancy was found to be associated to YKL-40 (Kelstrup et al., 2016).

Adiponectin has remarkable insulin sensitizing property (Tschritter et al., 2003) as well as antiatherogenic action (Li et al., 2009), thereby playing an important role in delaying and suppressing the metabolic derangements, which result in IR, T2DM, metabolic syndrome (Kim et al., 2013) and complications of diabetes including vascular (Li et al., 2009) and cardiac (Zhang et al., 2013) complications.

The current prospective comparative study aimed to evaluate the therapeutic yield of a lifestyle intervention consisted of dieting regimen and aerobic exercise with curcumin as herbal therapy on BMI, IR and estimated laboratory markers in obese and diabetic children.

Patients & Methods:-

The present study was conducted at Benha, Tanta and October 6 Universities since Sep 2014 till March 2016. After approval of the study protocol by the Local Ethical Committee and obtaining written fully informed parents' consent; 35 obese non-diabetic (Obese group) children and adolescents and 35 proved type-II diabetic children and adolescents (Diabetic group) irrespective of their body mass index were enrolled in the study.

All enrolled patients underwent determination of weight (kg) and height (cm) and body mass index (BMI) was computed as the weight in kilograms divided by the square of the height in meters according to last update of calculation model provided by Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic

Disease Prevention and Health Promotion. Obesity was defined according to the percentile of BMI adjusted for age and gender as follows: <85th percentile= average healthy weight, >85th-90th= at risk of being over-weight, >90th-95th percentile= over-weight and >95th percentile=obese (Cole et al., 2000). The study also included 20 control healthy weight children with BMI <85th percentile of BMI adjusted for age and gender and free of medical diseases or inflammatory conditions and without family history of diabetes especially for first-degree relatives (Control group). Diabetes mellitus was assured or excluded depending on estimation of fasting blood glucose (FBG) and fasting serum insulin (FSI).

Intervention program:-
During 12-weeks intervention program both diabetic and obese children underwent the following interventional items:

Aerobic fitness assessment:-
Subjects completed a continuous incremental $V.O_{2max}$ protocol on a bicycle ergometer (MedGraphics BreezeSuite Ultima CPX, St. Paul, MN; and Lode BV Corival Recumbent V2, Groningen, The Netherlands). Bicycle ergometer testing was selected because of the ease of administration, and maximal treadmill exercise is well tolerated in obese adolescents. Initial power output was 20 W, and was increased by 10-20 W/minute until volitional fatigue. Pedal rate was maintained between 60-100 rpm during the test. $V.O_{2max}$ was defined as the highest $V.O_2$ attained during the test when at least two of criteria were satisfied: 1) respiratory exchange rate >1, 2) heart rate (HR) >95% of age-predicted maximum, or 3) a plateau of $V.O_{2max}$. HR and blood pressure were monitored continuously during the test.

Exercise sessions:-
Sessions consisted of structured exercise including both aerobic and strength training three times weekly. Exercise consisted of 5–10 min for warm-up and stretching, followed by 15–30 min of cardiovascular exercise using treadmill or bicycle ergometer, 10–20 min of strength training using weight stack equipment, and 5–10 min of cool-down and stretching. Participants were started at 15 min of cardiovascular exercise and 10 min of strength training exercise and encouraged to progress by 2–3 min every week until 30 and 20 min, respectively, was achieved.

Lifestyle intervention:-
After baseline testing, all subjects began a structured 3-month lifestyle intervention consisting of dietary modification and exercise. Intensive dietary counseling was provided weekly for the first 4 wk of the intervention, monthly subsequently until 3 months. A target caloric deficit of ~250.500 cal/d was recommended throughout dietary counseling. Dietary regimen consisted of diets composed of nutrients contributing to total energy as 55% carbohydrate, 15% protein, and 30% fat. Other lifestyle changes included calorie restriction by exchanging high-calorie snacks with low-calorie and low-fat snacks; cutting down meal portions and frequency of snack consumption; limiting sugar-based carbonated drinks and limiting the duration of television watching (Zimmerman and Bell, 2010).

Herbal therapy:-
During the 12-week intervention program both diabetic and obese children received herbal therapy in the form of administration of curcumin 20 mg mixed with honey as a pellet to be taken three times daily. Dose of curcumin was adjusted according to the instruction of the University of Michigan Health System (Aronson, 2011).

Laboratory measurements:-
Fasting venous blood samples were obtained under complete aseptic conditions from the antecubital vein. Blood sample was divided into 2 parts:

1. The first part was put in a tube containing sodium fluoride (2 mg sodium fluoride/ ml blood) to prevent glycolysis and plasma was separated by centrifugation for estimation of fasting blood glucose (FBG) by glucose oxidase method (Tinder, 1969).
2. The second part was put in a plane container and left to clot at room temperature for 30 minutes before centrifugation for 20 minutes at 1,000g. Freshly prepared serum was stored at –20^{o}C till ELISA estimation of insulin concentrations (Enzymuntest Insulin, ES 600, Boehringer Mannheim) (Andersen et al., 1993), progranulin (Human progranulin, AdipoGen Inc., Seoul, Korea) (Bhandari et al., 1992), TNF-α (ELISA kit from Pelikine™ Inc., Concord, USA) (De Kossodo et al., 1995), adiponectin (Abcam's Human Adiponectin ELISA, San Francisco, USA) (Yokota et al., 2000) and YKL-40 levels (Human Chitinase 3-like 1/YKL-40 PicoKine ™ ELISA Kit, Valley Ave, Pleasanton, USA) (Shackelton et al., 1995).

Evaluation of insulin resistance (IR):-
Insulin resistance was measured by homeostasis model assessment (HOMA). The HOMA-IR score was calculated as (fasting serum insulin (μU/ml) x [fasting plasma glucose (mg/ml)/18])/22.5; HOMA-index >2 is considered abnormal (Matthews et al., 1985).

Follow-up:-
Body weight (BW), calculated BMI and HOMA-IR score and laboratory investigations were determined at time of start of intervention and at the end of the 12-weeks intervention program.

Statistical analysis:-
Obtained data were presented as mean±SD, ranges, numbers and ratios. Considering gender and age difference of white adipose tissue secretion of adipokines (Haluzik, 2005), estimated serum levels of studied adipokines were represented by Median Interquartile range. Results were analyzed using One-way ANOVA with post-hoc Tukey HSD Test and Chi-square test (X^2 test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

Results:-
The study included 35 obese children; 23 males and 12 females and 35 diabetic children; 21 males and 14 females with mean age of 12±1.9; range: 7-17 years and 20 controls; 11 males and 9 females of mean age of 12±2; range: 8-15 years. There was non-significant inter-group difference as regards age and gender distribution.

Baseline data showed significantly higher BW and BMI of study children compared to control children with non-significantly higher measures of diabetic children compared to obese children. At the end of intervention, both obese and diabetic children had lost weight with significant difference compared to baseline BW. Mean percentage of decrease of BMI was 13.8 and 12.8% of baseline BMI in obese and diabetic children, respectively. Details of BMI data and its changes are shown in table I.

Baseline insulin resistance (IR) parameters were significantly higher in patients compared to controls and in diabetic compared to obese patients. The applied intervention program significantly improved insulin sensitivity as manifested in both groups by significant reduction of IR parameters determined at the end of 12-w intervention compared to baseline IR data, despite being still significantly higher compared to control data. The response to the intervention program was more pronounced in obese than in diabetic patients as manifested by significantly reduced IR parameters in obese than in diabetics. Also, at the end of 12-w intervention no obese children, but 16 diabetic children had HOMA-IR index >2 with significantly higher frequency of patients had HOMA-IR index >2 at enrolment compared to at the end of the 12-w intervention. Details of measurements of IR parameters are shown in table II.

Mean baseline serum levels of PGRN, YKL-40 and TNF-α were significantly higher in patients compared to controls with significantly higher levels in diabetic compared to obese patients. On contrary, mean baseline serum adiponectin levels were significantly lower in patients compared to controls with non-significantly lower levels in diabetic compared to obese patients.

At the end of 12-weeks intervention, serum PGRN and YKL-40 levels were significantly decreased in comparison to their baseline levels, despite being still significantly higher than control levels. However, serum PGRN and YKL-40 levels were significantly lower in obese compared to diabetics. As regards, serum levels of TNF-α estimated at the end of 12-w intervention were still significantly higher in patients than in controls and in diabetics than in obese patients. In comparison to baseline levels, serum levels of and TNF-α estimated at the end of the intervention were significantly lower in obese but non-significantly lower in diabetics.

On the other hand, serum adiponectin levels estimated at the end of the intervention were significantly lower in diabetics and non-significantly lower in obese compared to control levels. However, serum adiponectin estimated at end of intervention were significantly higher in obese and non-significantly higher in diabetics compared to their respective baseline levels with significantly higher levels in obese compared to diabetics. Details of laboratory findings of studied groups are shown in table III.

Discussion:-

The current study detected significantly higher BMI and HOMA-IR index, and estimated serum levels of progranulin (PGRN), YKL-40 and TNF-α with significantly lower serum adiponectin levels in obese and diabetic children compared to control children. These findings were in hand with previous literature detected significantly higher YKL-40 levels in type-2 diabetics (Nielsen et al., 2008) and type-2 obese diabetics (Catalán et al., 2011; Thomsen et al., 2015) than normo-glycemic lean subjects and in obese children with insulin resistance (IR) than in non-IR obese children (Kyrgios et al., 2012). Also, Youn et al. (2009) reported significantly higher PGRN serum levels in T2DM patients compared to normo-glycemics. Moreover, the obtained results were in line with previous work detected significantly higher YKL-40 (Brix et al., 2011) and PGRN (Li et al., 2014; Xu et al., 2015) in complicated diabetics than in non-complicated diabetics.

Baseline levels of estimated serum markers showed significant correlations with HOMA-IR index; thus indicating a relationship between obesity and/or diabetes and disturbed serum levels of adipo-cytokines. In line with such relations; Nielsen et al., (2008) found plasma YKL-40 levels were associated with FBG and plasma interleukin (IL)-6 levels; Hempen et al., (2009) reported that YKL-40 was correlated with HOMA-IR variables (fasting insulin and FBG), thus indicating its role in developing IR and T2DM. Also, Catalán et al. (2011) found that level of YKL-40 was associated with variables of IR and inflammation and Kyrgios et al. (2012) found serum YKL-40 levels were positively correlated with age, BMI, HOMA-IR index and WBC count, but HOMA-IR index remained significantly associated with YKL-40 levels after adjustment for other factors

Similarly, Youn et al. (2009) detected correlation between circulating PGRN serum levels and BMI, macrophage infiltration in omental adipose tissue, CRP and total cholesterol concentrations and Li et al. (2014) found serum PGRN levels were correlated positively with BMI, waist circumference, IR variables, glycated hemoglobin A1c, triglyceride, and HOMA-IR, and were inversely related to HDL levels. Xu et al. (2015) found serum PGRN levels were positively and markedly correlated with disease duration, BMI, and triglyceride, IL-6, and TNF-α serum levels.

Intervention 12-week program changed the picture with significant decrease of the elevated BMI, HOMA-IR index and PGRN, YKL-40 and TNF-α serum levels, but significantly elevated the decreased adiponectin serum levels. In line with these findings; Catalán et al. (2011) found that elevated circulating levels of YKL-40 were decreased after weight loss following a conventional hypocaloric diet. Youn et al. (2009) found physical training significantly reduces elevated PGRN levels in T2DM patients. Carrel et al. (2009) suggested that the school-based fitness oriented curriculum resulted in improved insulin sensitivity with decreased serum levels of inflammatory markers. Blüher et al. (2012) found adiponectin; HDL, high-sensitivity CRP and PGRN displayed continued, cumulative significant improvement compared with baseline measures.

Nemet et al. (2014) reported that BW, BMI, and BMI percentiles of obese children were significantly reduced and endurance time significantly increased following the 3 months combined nutritional-behavioral-physical activity intervention. Wang et al. (2015) documented that in obese children the addition of aerobic exercise training to caloric restriction increased plasma adiponectin concentrations significantly than caloric restriction alone.

Starting structural exercise in conjunction with dietary regimen during the applied intervention could abolish the deleterious effects of weight reduction on muscle mass and contribute to obtain acceptable body countering which alleviates the psychological impact of obesity so pushing the child to continue the program. In support of such policy; Chomentowski et al. (2009) documented that diet-induced weight loss significantly decreased muscle mass, however, the addition of moderate aerobic exercise attenuated the loss of muscle mass. Sgro et al. (2009) suggested that an 8-week resistance training program is sufficient time to significantly change body composition, strength, and power measures in overweight or obese children. Also, Carrel et al. (2009) suggested that the school-based fitness oriented curriculum resulted in improved body composition and muscle mass.

Brambilla et al. (2011) documented that both diet and physical activity contribute to fat loss, but only physical activity affects fuel metabolism through increased fat oxidation causing prevention of IR or restoration of insulin sensitivity and increases muscle mass. You et al. (2013) documented that exercise training in obese individuals reduces chronic inflammation. Also, Garnett et al. (2014) reported that exercise program reduced BMI and percent of body fat with increased insulin sensitivity index in obese adolescents at risk of T2DM in dependent on the extent of diet restriction. Also, Blüher et al. (2014) found the one-year combined exercise/lifestyle program significantly improved markers of obesity with glycemic control.

In trial to explore the underlying mechanisms for the beneficial effect of the applied intervention program; Wang et al. (2015) found aerobic exercise training caused increased adiponectin release from abdominal and gluteal subcutaneous adipose tissue. You et al. (2013) attributed the beneficial effect of exercise training to its effect on generation of muscle-derived anti-inflammatory 'myokine', improved adipose tissue hypoxia and reduction of local adipose tissue inflammation, leukocyte adhesion and number of pro-inflammatory cells and pro-inflammatory cytokine production per cell.

Na et al. (2014) found curcuminoids supplementation of typ-2 diabetics for 3-months led to significant decreases in serum levels of CRP, TNF-α and IL-6. Panzhinskiy et al. (2014) attributed the alleviating effect of curcumin on obesity-induced glucose intolerance to a novel curcuminoid which was found to augment insulin signaling, lower the endoplasmic reticulum stress, reverse palmitate-induced impairment of insulin signaling and resulted in higher energy expenditure without altering the respiratory quotient. As another mechanism; Ghorbani et al. (2014) attributed the curcumin induced reduction of blood glucose level to reducing hepatic glucose production, suppression of hyperglycemia-induced inflammatory state, stimulation of glucose uptake by up-regulation of glucose transmitters' genes expressions, activation of AMP kinase, improvement in pancreatic cell function and stimulation of insulin secretion, thus reducing IR.

It could be concluded that obesity, T2DM and disturbed adipokines serum levels constitute a vicious circle entrapping children. The proposed intervention program consisting of dietary restriction, structured aerobic exercise and curcumin significantly reduced body weight and insulin resistance and ameliorated disturbance of adipokines serum levels in obese and diabetic children. Continued application of the program may be advocated for achieving progressive resolution of obesity and control of diabetes and pro-inflammatory adipokines.

Table I: BMI of enrolled children determined at time of enrolment and at end of intervention and percentage of BMI change

Parameters		Control	Obese	Diabetics
Baseline	Weight (kg)	38.5±7.1	62.4±5.2	63.6±6.6
			P1=0.001	P1=0.001 P2=0.003
	Height (cm)	142±11.3	147±9.3	144.3±8.9
			P1=0.064	P1=0.821 P2=0.11
	BMI (kg/m^2)	19±2.3	29±3	30.7±3.5
			P1=0.001	P1=0.001 P2=0.239
End of intervention	Weight (kg)	38.5±7.1	60.6±7	55.4±8.1
			P1=0.001	P1=0.001 P2=0.029
	BMI (kg/m^2)	19±2.3	27.4±3.2	26.6±3
			P1=0.001 P3=0.001	P1=0.001 P2=0.482 P3=0.001
% of change of BMI at end of intervention			13.8±5.8	12.8±6.3
				P2=0.492

Data are presented as mean±SD; BMI: Body mass index; P1: significance of difference versus control group; P2: significance of difference versus obese group; P3: significance of difference baseline data of each group; $p<0.05$ indicates significant difference

Table II: HOMA-IR data of enrolled children determined at time of enrolment and at end of intervention and percentage of BMI change

Parameters		Control	Obese	Diabetics
Baseline	FBG (mg/dl)	82.9±8.4	116.9±5.3	146.1±12.4
			P1=0.001	P1=0.001 P2=0.001
	FI (μIU/L)	2.2±0.3	4.45±1.46	6.25±0.8
			P1=0.001	P1=0.001 P2=0.001
	HOMA-IR index	0.44±0.1	1.29±0.46	2.25±0.32
			P1=0.001	P1=0.001 P2=0.001
End of intervention	FBG (mg/dl)	82.9±8.4	113.9±3.4	138.2±9.3
			P1=0.001 P3=0.005	P1=0.001 P2=0.001 P3=0.004
	FI (μIU/L)	2.2±0.3	3.66±1.22	5.28±0.73
			P1=0.001 P3=0.016	P1=0.001 P2=0.001 P3=0.001
	HOMA-IR index	0.44±0.1	1.04±0.37	1.8±0.32
			P1=0.001 P3=0.012	P1=0.001 P2=0.001 P3=0.001
Frequency of patients with HOMA-IR >2	Enrolment time		9 (25.7%)	25 (71.4%)
	End of intervention		0	16 (45.7%)
				P2=0.023

Data are presented as mean±SD; FBG: Fasting blood glucose; FI: Fasting serum insulin; HOMA-IR: Homeostasis model assessment- insulin resistance; P1: significance of difference versus control group; P2: significance of difference versus obese group; P3: significance of difference baseline data of each group; $p<0.05$ indicates significant difference

Table III: Laboratory findings determined at time of enrolment and end of intervention

Parameters		Control	Obese	Diabetics
Baseline	PGRN (pg/ml)	185 (165-210)	215 (196.5-251.5)	295 (265-317.5)
			P1=0.001	P2=0.001 P3=0.001
	YKL-40 (pg/ml)	43.9 (42.53-51.9)	69.4 (58.85-75.1)	78.3 (74.1-82.7)
			P1=0.001	P2=0.001 P3=0.001
	TNF-α (pg/ml)	12.15 (9.5-13.9)	16.9 (12.5-21)	20.6 (18.3-24)
			P1=0.001	P2=0.001 P3=0.001
	Adiponectin (µg/ml)	8 (6.75-9.25)	6 (5-7)	4 (4-7)
			P1=0.0018	P2=0.001 P3=0.077
End of intervention	PGRN (pg/ml)	185 (165-210)	179 (167.4-210.1)	255.1 (223.7-269.7)
			P1=0.001 P4=0.001	P2=0.001 P3=0.001 P4=0.001
	YKL-40 (pg/ml)	43.9 (42.53-51.9)	59.2 (49.8-65.35)	70.2 (66.4-73.1)
			P1=0.001 P4=0.001	P2=0.001 P3=0.001 P4=0.001
	TNF-α (pg/ml)	12.15 (9.5-13.9)	13.2 (10.9-14.2)	18.6 (14.2-21.85)
			P1=0.604 P4=0.001	P2=0.001 P3=0.001 P4=0.053
	Adiponectin (µg/ml)	8 (6.75-9.25)	7.25 (6.125-8)	5 (4.7-8)
			P1=0.288 P4=0.0077	P2=0.0013 P3=0.038 P4=0.070

Data are presented as median value; inter-quartile ranges are in parenthesis; PGRN: progranulin; TNF-α: tumor necrosis factor-α; YKL-40: Chitenase-like protein; P1: significance of difference versus control group; P2: significance of difference versus obese group; P3: significance of difference baseline data of each group; P4: significance versus baseline levels; $p<0.05$ indicates significant difference

Conflict of interest:-
No conflict of interest

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