The Impact of Obesity on Some Hormones and the Cognitive Function among School Girls

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Abstract: The number of obese children has increased considerably worldwide and childhood obesity causes many problems that can track into adulthood. The current study was conducted on 45 obese girls [mean age±SE =10.53±1.29 years; mean BMI±SE =28.43± 4.62 Kg/m^2] in addition to 45 age- and sex-matched controls (mean age±SE =10.36±1.53 years; mean BMI±SE =19.07±3.47 Kg/m^2). Estimation of serum ghrelin and growth hormone (GH), plasma leptin, insulin, and insulin-like growth factor-1 (IGF-1) as well as learning ability and cognitive functions (auditory vigilance, digit span, coding ability and visual memory) were carried out. The levels of plasma leptin, insulin and IGF-1 were highly significantly higher whereas those of serum ghrelin and GH were highly significantly lower in the obese group than the control. The total right response of auditory vigilance (TR) showed insignificant decrease while the total wrong response of auditory vigilance (TW) showed significant increase in the obese group as compared with the control group. Digit span showed highly significant decrease while coding scores showed significant increase. Visual memory recall showed insignificant decrease while visual memory classification showed highly significant decrease in the obese group as compared with the control group. Ghrelin decreased because of hyperinsulinemia and hyperleptinemia. Increased leptin level may be due to increased amount of adipose tissue in obese subjects. Hyperinsulinemia occurs to compensate for insulin resistance occurring in obesity and to maintain glucose homeostasis. The decrease in GH may be due to low GHRH, high somatostatin and increased free IGF-1 levels. Increased IGF-1 in obese subjects may be a result of hyperinsulinemia. Obesity in school girls negatively affected the levels of the measured hormones as well as the educational achievements of these girls which reflect the impact of obesity on cognitive performance and learning ability in these subjects. [New York Science Journal 2010;3(4):66-71]. (ISSN: 1554-0200).

Key words: obesity, girls, ghrelin, leptin, insulin, GH, IGF-1, cognition

1. Introduction

The number of obese children and adolescents worldwide has increased considerably (Ogden *et al.*, 2002). An epidemic of obesity is being observed in most societies around the world (Reich *et al.*, 2003). The highest prevalence rates of childhood obesity have been observed in developed countries, however, its prevalence is increasing in developing countries as well. The prevalence of overweight and obesity in girls was significantly higher than that in boys (Kelishadi *et al.*, 2003). Using the Centers for Disease Control (CDC) cutoffs for BMI, 12.1 percent of Egyptian adolescents were overweight, and 6.2 percent were obese (Salazar-Martinez *et al.*, 2006). Over two thirds of children aged 10 and older who are obese will become obese adults, and the rise in medical complications in adults is mirrored in children. Therefore, obese children and adolescents tend to develop serious medical and psychosocial complications either at the present time or later on in their life, and have a greater risk of adult morbidity and mortality (Huang *et al.*, 2004).

Ghrelin, a peptide first identified as an endogenous GH secretagogue (GHS) (Kojima *et al.*, 1999), is a powerful orexigen, stimulating food intake through GH-independent mechanisms (Nakazato *et al.*, 2001). Ghrelin appears to mediate its effects at least in part by stimulating NPY/AgRP-expressing neurons in the arcuate nucleus (ARC) (Horvath *et al.*, 2001). Carlini *et al.* (2004) demonstrated that ghrelin is able to modulate cognitive processes not only in the hippocampus but elsewhere; in particular, ghrelin enhanced memory on an avoidance task following administration to different brain areas.

Leptin, a product of leptin gene, was discovered in 1994 by Friedman and colleagues. Leptin gene is a protein of molecular weight 18,000, containing a signal sequence which is cleaved to produce the mature hormone of molecular weight 16,000 (Zhang *et al.*, 1994). Leptin is not only synthesized by the white adipose tissue, but it is also produced in several other sites like brown adipose tissue, stomach, placenta, mammary gland, ovarian follicles and certain fetal organs such as heart and bone or cartilage and perhaps even the brain (Trayhurn *et al.*, 2001). Leptin is an anorectic peptide and its anorectic effect is mediated by the activation of the proopiomelanocortin (POMC) neurons, which increase α-melanocyte-stimulating hormone (α-MSH), a central nervous system (CNS) peptide that inhibits feeding. Simultaneously leptin

suppresses neuropeptide Y (NPY) and agouti-related protein (AgRP), which may also contribute to decreased feeding (Knecht *et al.*, 2008).

Memory impairment has been associated with obesity (Farr *et al.*, 2004). Leptin improved memory and this suggested that the resistance to leptin in the brain may play a part in the memory impairment seen with obesity (Farr *et al.*, 2006). Also, Morrison (2009) reported that leptin improves learning, memory and other forms of cognition.

Insulin which is an afferent signal circulating in proportion to adipose tissue mass exerts many central actions similar to those of leptin (Schwartz *et al.*, 2000). Selective elimination of insulin receptors from the CNS causes hyperphagia and fat accumulation (Obici *et al.*, 2000), whereas insulin agonists that preferentially partition into the brain exert the opposite effects (Air *et al.*, 2002). When body weight augments, insulin resistance occurs with attendant increase in insulin secretion. The hormone enters the brain in proportion to its circulating levels, contributing to reduce energy intake through the activation of catabolic pathways (Schwartz *et al.*, 2000). Insulin and leptin both activate POMC neurons and therefore inhibit appetite (Wanting *et al.*, 2005).

In human obesity, the GH/IGF-1 axis is altered that basal GH secretion is blunted, with reduced GH half-life, frequency of secretory episodes, and daily production rate (Veldhuis *et al.*, 1991). Also, binding of IGF-1 to its receptor is decreased (Hochberg *et al.*, 1992). Thus, human obesity may be seen as a condition characterized by an increase in both sensitivity to GH and resistance to IGF-1 (De Marinis *et al.*, 2004). The binding sites for GH and IGF-1 are found in various areas of the brain. Their distribution suggests that GH and IGF-1 contribute to the function of the hippocampus, a brain structure important for the maintenance of cognitive functions such as learning and memory. Evidence for cognitive deficits in GH-deficient individuals has been found in various studies, some of which have shown that these deficits can be reversed by GH substitution therapy (van Dam *et al.*, 2000).

Objective: The main purpose of the current study was to investigate the effect of obesity on the levels of some hormones as well as learning ability and cognitive function of elementary school girls.

2. Subjects and Methods

Research Design and Methods

For this study, 45 Egyptian girls with simple obesity and 45 age- and sex-matched controls were recruited from 4 elementary schools in Dokki region, Giza governorate, Egypt. Their ages ranged from 8 to 12 years. Anthropometric measurements and memory and learning tests were done to every subject, a questionnaire for the social information was answered by parents. Fasting blood samples were taken for measurements of hormones.

1. Study Population

The participation rate was 44% of the subjects initially selected. To determine whether subjects presented previous diseases, an appropriate questionnaire was administered. Subjects recruited were in good health and with no known diseases. None of both control and obese girls had a chronic illness, such as treated arterial hypertension, diabetes mellitus, heart failure or chronic hepatic failure. Also, none of them was anemic. None of the girls was taking medication. Informed consent was obtained from girls' parents before taking part in our study. The protocol was approved by the Ethical Committee of the National Research Centre, Dokki, Giza, Egypt. The clinical examinations were performed during fasting and after emptying the urinary bladder.

2- Anthropometry and Body Composition

The measurements were carried out in 4 elementary schools between September, 2008 to Jan, 2009. The schools were randomly selected from Dokki, Giza governorate, Egypt. BMI was calculated as weight in kilograms divided by height in meters squared. Normal weight children were defined as having a BMI $\leq 85^{th}$ percentile. Obesity was defined as a BMI $\geq 95^{th}$ percentile, for age and sex according to Ogden *et al.* (2002).

Height (Ht) was measured to the nearest 0.5 cm on a wall-mounted Harpenden's stadiometer. Weight (Wt) was determined to the nearest 0.1 kg on a standard medical balance scale, with the subject dressed only in light underwear and no shoes. Waist (midway between the 10^{th} rib and the iliac crest) and hip (greater femoral trochanter) circumference (WC and HC) were measured using a non-stretchable tape measure in a standing position. Body composition was determined by a bioelectrical impedance analyzer using a formula provided by the manufacturers and percent fat mass (FM%) was calculated. Also weight for age and height for age parameters (percent median, Z-score and percentile) were calculated.

3- Tests of Cognition:

The total right response of auditory vigilance (TR) and the total wrong response of auditory vigilance (TW) were measured. Also, digit span test was done. In addition, coding ability test and visual memory test (visual memory recall and visual memory classification) were carried out according to Wechsler.

4- Hormone Measurements:

Blood samples were obtained in the morning after an overnight fast, and plasma as well as serum samples were separated using cooling centrifuge (4˚C) for 15 min. at 3000 rpm for hormones measurements. Serum ghrelin was measured by an enzyme-linked immunosorbent assay (ELISA) kit (Phoenix Pharmaceuticals, Inc., USA) according to the method of Porstmann and Kiessig (1992). Plasma leptin was measured using an ELISA kit (DRG Instruments GmbH, Germany) according to the method of Considine *et al.* (Considine *et al.*, 1996). Plasma insulin was measured using an ELISA kit (DRG Instruments GmbH, Germany) according to the method of Judzewitsch *et al.* (1982). Serum Growth GH was assayed using an ELISA kit (Phoenix Pharmaceuticals, Inc., USA) according to the method of Underwood *et al.* (1994). Plasma IGF-1 was determined using an ELISA kit (DRG Instruments GmbH, Germany) according to the method of Schneiderman *et al.* (1994).

Statistical Analysis:

All statistical analyses were performed using version 14 of the computer-based statistical package of Statistical Product and Service Solutions (SPSS). Student t-test and Pearson's correlation were performed to compare groups and detect the possible relationships between hormones and other measurements. Also, multiple stepwise regression analysis was done to show the most predicting parameter of obesity considering either BMI or FM% as the dependent variable.

3. Results

Table (1) shows descriptive statistics as means (±SE) and P values of the anthropometric measurements in the control and obese groups. All anthropometric measurements were highly significantly increased (P<0.01) in the obese group as compared with the control group, except for Ht which showed significant increase (P<0.05) and Ht-for-age parameters (% median, Z-score and percentile) which showed insignificant increase (P>0.05).

Table (1): Anthropometric parameters of control and obese groups

Groups / Parameters	Control (n = 45) Mean ± SE	Obese (n = 45) Mean ± SE
Wt (Kg)	39.211 ± 1.414	61.333 ± 1.977**
Ht (cm)	142.618 ± 1.352	147.778 ± 1.554*
BMI (Kg/m^2)	19.065 ± 0.518	28.430 ± 0.689**
FM%	21.194 ± 1.520	33.144 ± 1.011**
WC (cm)	69.711 ± 0.960	83.133 ± 1.325**
HC (cm)	82.200 ± 0.829	98.231 ± 1.806**
Waist/Ht	0.490 ± 0.007	0.563 ± 0.008**
WHR	0.847 ± 0.005	0.850 ± 0.010
Wt-for-age (% median)	107.891 ± 1.457	184.296 ± 18.863**
Wt-for-age (z-score)	0.294 ± 0.061	2.733 ± 0.216**
Wt-for-age (percentile)	60.776 ± 2.217	98.013 ± 0.343**
Ht-for-age (% median)	99.642 ± 0.663	101.296 ± 0.580
Ht-for-age (z-score)	-0.091 ± 0.146	0.263 ± 0.126
Ht-for-age (percentile)	48.998 ± 3.940	58.758 ± 4.012

Asterisks indicate significant differences between the two groups (*) $P<0.05$, (**) $P<0.01$
Wt= weight, Ht= height, BMI= body mass index, FM%= fat mass percent, WC= waist circumference, HC= hip circumference, WHR= waist to hip ratio.

The results in table (2) depict that the levels of plasma leptin, insulin and IGF-1 showed highly significant increase (P<0.01) while those of serum ghrelin and GH showed highly significant decrease (P<0.01) in the obese group as compared with the control group.

Table (2): Levels of hormones in control and obese groups

Group / Parameters	Control (n= 45) Mean ± SE	Obese (n= 45) Mean ± SE
Ghrelin (ng/ml)	3.416 ± 0.094	2.698 ± 0.076**
Leptin (ng/ml)	9.667 ± 0.415	40.556 ± 0.886**
Insulin (µIU/ml)	16.289 ± 0.533	35.556 ± 0.886**
GH (ng/ml)	4.246 ± 0.089	1.903 ± 0.079**
IGF-1 (ng/ml)	87.467 ± 2.021	95.133 ± 2.611*

Asterisks indicate significant differences between the two groups (*) $P<0.05$, (**) $P<0.01$
GH= growth hormone, IGF-1= insulin-like growth factor-1

Data in table (3) shows the results of the control and obese groups represented as means±SE. TR showed insignificant decrease (P>0.05) while TW showed significant increase (P<0.05) in the obese girls as compared with control girls. Digit span showed highly significant decrease (P<0.01) however coding score showed significant increase (P<0.05) in the obese girls as compared with control girls. Visual memory recall showed insignificant decrease (P>0.05) and Visual memory classification showed highly significant decrease (P<0.01) in the obese group when compared with the control group.

Table (3): Cognitive tests of control and obese groups

Groups / Parameters	Control (n= 45) Mean ± SE	Obese (n= 45) Mean ± SE
TR	40.489 ± 0.269	39.711 ± 0.421
TW	1.511 ± 0.269	2.511 ± 0.416*
Digit span	13.867 ± 0.689	10.822 ± 0.724**
Coding	12.089 ± 0.256	13.244 ± 0.372*
Visual Memory Recall	10.600 ± 0.630	10.489 ± 0.362
Visual Memory Classification	8.111 ± 0.264	6.222 ± 0.246**

Asterisks indicate significant differences between the two groups (*) $P<0.05$, (**) $P<0.01$
TR= total right response of auditory vigilance test, TW= total wrong response of auditory vigilance test

Table (4) presents Pearson's correlation between hormones and anthropometric measurements in the control group. It appears that there was insignificant correlation (P>0.05) between these measurements.

Table (4): Pearson's correlation between the levels of hormones and anthropometric parameters in the control group

Parameters	Wt	Ht	BMI	WC	HC	FM %	Waist/Ht	WHR	Wt-for-age (% median	Wt-for-age (Z-score)	Wt-for-age (Percentile)	Ht-for-age (% median	Ht-for-age (Z-score)	Ht-for-age (Percentile)
Ghrelin	-0.037	-0.058	-0.019	0.068	0.020	0.226	0.101	0.115	-0.044	-0.063	-0.066	-0.038	-0.033	-0.056
Leptin	-0.010	-0.166	0.095	0.187	0.089	0.113	0.286	0.276	0.035	0.039	0.042	-0.172	-0.166	-0.168
Insulin	-0.061	-0.115	-0.005	0.276	0.351	-0.078	0.339	0.047	0.092	0.109	0.116	0.013	0.029	-0.068
GH	-0.008	0.060	-0.076	0.069	0.109	0.236	0.023	-0.030	0.206	0.208	0.202	0.278	0.278	0.260
IGF1	0.116	0.042	0.156	0.059	0.033	0.130	0.041	0.095	-0.096	-0.112	-0.115	-0.266	-0.262	-0.218

Data are expressed as correlation coefficient (r) values

Table (5) presents Pearson's correlation between hormones and anthropometric measurements in the obese group. The results show highly significant negative correlation (P<0.01) between serum ghrelin and Wt, BMI, WC, HC, waist/Ht and Z-score and percentile for Wt-for-age and significant negative correlation (P<0.05) with % median for Wt-for-age. Plasma leptin level showed highly significant positive correlation (P<0.01) with Wt, BMI, WC, HC, waist/Ht and Z-score for Wt-for-age. Also, it showed significant positive correlation (P<0.05) with % median for Wt-for-age and FM%. Highly significant positive correlation (P<0.01) was found between plasma insulin and Wt, BMI, WC, HC, waist/Ht ratio as well as Wt-for-age parameters (% median, Z-score and percentile). Serum GH showed highly significant negative correlation (P<0.01) with Wt, BMI, WC, HC, waist/Ht ratio as well as Z-score and percentile for Wt-for-age and significant negative correlation (P<0.01) with % median for Wt-for-age. Plasma IGF-1 level showed highly significant positive correlation (P<0.01) with Wt, BMI, WC, HC, waist/Ht ratio as well as Wt-for-age parameters (% median, Z-score and percentile).

Table (5): Pearson's correlation between the levels of hormones and anthropometric parameters in the obese group

Parameters	Wt	Ht	BMI	WC	HC	FM %	Waist/Ht	WHR	Wt-for-age (% median	Wt-for-age (Z-score)	Wt-for-age (Percentile)	Ht-for-age (% median	Ht-for-age (Z-score)	Ht-for-age (Percentile)
Ghrelin	-0.748**	-0.275	-0.826**	-0.676**	-0.694**	-0.105	-0.566**	0.112	-0.375*	-0.577**	-0.529**	0.183	0.183	0.208
Leptin	0.587**	0.235	0.608**	0.535**	0.531**	0.295*	0.429**	-0.027	0.339*	0.460**	0.258	-0.112	-0.110	-0.135
Insuli	0.71	0.25	0.81	0.65	0.66	0.07	0.55	-	0.38	0.59	0.52	-	-	-

n	4**	2	2**	1**	8**	9	5**	0.102	0**	5**	5**	0.139	0.147	0.173
GH	-0.686**	-0.288	-0.753**	-0.596**	-0.627**	-0.071	-0.472**	0.125	-0.351*	-0.513**	-0.490**	0.211	0.209	0.232
IGF1	0.847**	0.258	0.915**	0.756**	0.726**	0.007	0.655**	-0.071	0.643**	0.770**	0.478**	-0.209	-0.215	-0.234

Data are expressed as coefficient of variation (r) values, asterisks indicate significant differences (*) $P<0.05$, (**) $P<0.01$

Table (6) presents Pearson's correlation between the tests of cognition and anthropometric measurements in the control group. TR showed highly significant negative correlation (P<0.01) while TW showed highly significant positive correlation (P<0.01) with FM%. Coding scores showed highly significant negative correlation with Waist/Ht ratio (P<0.01) and significant negative correlation (P<0.05) with Wt-for-age parameters (% median, Z-score and percentile). Visual memory recall showed highly significant positive correlation with Wt, Ht, BMI, WC, HC (P<0.01) while it showed highly significant negative correlation (P<0.01) with Ht-for-age parameters (% median, Z-score and percentile). Visual memory classification showed highly significant negative correlation (P<0.01) with Waist/Ht ratio and Wt-for-age parameters (% median, Z-score and percentile).

Table (6): Pearson's correlations between cognition tests and anthropometric measurements in the control group

Parameters	Wt	Ht	BMI	WC	HC	FM%	Waist/Ht	WHR	Wt-for-age (% median)	Wt-for-age (Z-score)	Wt-for-age (Percentile)	Ht-for-age (% median)	Ht-for-age (Z-score)	Ht-for-age (Percentile)
TR	-0.075	-0.094	-0.034	-0.166	-0.239	-0.500**	-0.088	0.020	-0.143	-0.091	-0.085	-0.068	-0.073	-0.013
TW	0.075	0.094	0.034	0.166	0.239	0.500**	0.088	-0.020	0.143	0.091	0.085	0.068	0.073	0.013
Digit span	0.037	-0.019	0.068	0.069	0.017	0.058	0.068	0.129	0.201	0.200	0.205	0.052	0.044	0.094
coding	0.035	0.234	-0.088	-0.250	-0.247	0.067	-0.388	-0.144	-0.307	-0.355	-0.364	-0.074	-0.065	-0.042
Recall	0.600**	0.460**	0.528**	0.420**	0.424**	0.106	0.105	0.251	0.215	0.139	0.123	-0.460**	-0.446**	-0.438**
Classification	-0.076	0.190	-0.185	-0.290	-0.224	0.124	-0.377**	-0.274	-0.522**	-0.559**	-0.560**	-0.062	-0.052	-0.065

Data are expressed as coefficient of variation (r) values, asterisks indicate significant differences (**) $P<0.01$

Table (7) illustrates Pearson's correlation between the tests of cognition and anthropometric measurements in the obese group. Significant negative correlation (P<0.05) between TW and Wt was found. Digit span showed highly significant positive correlation (P<0.01) with FM%. Coding scores showed highly significant negative correlation (P<0.01) with Wt, WC and HC, and it showed significant negative correlation (P<0.05) with Ht.

Table (7): Pearson's correlations between cognition tests and anthropometric measurements in the obese group

Parameters	Wt	Ht	BMI	WC	HC	FM%	Waste/Ht	WHR	Wt-for-age	Wt-for-age	Wt-for-age	Ht-for-age	Ht-for-age	Ht-for-age

									(% median	(Z-score)	(Percentile)	(% median	(Z-score)	(Percentile)
TR	0.260	0.229	0.163	0.270	0.252	0.151	0.136	-0.011	0.017	-0.008	-0.075	-0.145	-0.138	-0.123
TW	-0.314*	-0.275	-0.204	-0.283	-0.276	-0.151	-0.117	0.027	-0.046	-0.061	-0.088	0.067	0.063	0.036
Digit span	0.189	0.261	0.237	0.167	0.287	0.447**	0.031	-0.130	0.016	0.113	0.208	-0.125	-0.126	-0.088
coding	-0.484**	-0.304*	-0.290	-0.445**	-0.439**	-0.077	-0.249	0.052	-0.135	-0.074	0.207	0.182	0.169	0.190
Recall	0.081	0.181	-0.023	-0.014	0.192	0.280	-0.156	-0.258	-0.062	-0.163	-0.149	-0.175	-0.166	-0.167
Classification	-0.006	0.062	-0.036	-0.115	-0.045	0.024	-0.172	-0.140	0.039	-0.070	-0.199	-0.187	-0.176	-0.176

Data are expressed as coefficient of variation (r) values, asterisks indicate significant differences (*) $P<0.05$, (**) $P<0.01$

The data in table (8) represent Pearson's correlation among the levels of hormones in the control group. Significant negative correlation (P<0.05) was found between serum GH and plasma IGF-1 levels while significant positive correlation (P<0.05) between plasma leptin and serum GH levels has been recorded.

Table (8): Pearson's correlations among the levels of hormones in the control group

Parameters	GH	IGF1	Leptin	Ghrelin	Insulin
Ghrelin	0.111	0.080	0.190	1.000	0.218
Leptin	0.306*	0.060	1.000	0.190	0.042
Insulin	-0.014	0.127	0.042	0.218	1.000
GH	1.000	-0.338*	0.306*	0.111	-0.014
IGF1	-0.338*	1.000	0.060	0.080	0.127

Data are expressed as coefficient of variation (r) values, asterisks indicate significant differences (*) *P<0.05*

Table (9) presents Pearson's correlation among the levels of hormones in the obese group. Serum ghrelin level showed highly significant negative correlation (P<0.01) with plasma leptin, insulin and IGF-1 while it showed highly significant positive correlation (P<0.01) with serum GH level. Plasma leptin level showed highly significant positive correlation (P<0.01) with plasma insulin and IGF-1 while it revealed highly significant negative correlation (P<0.01) with serum GH level. Plasma insulin level showed highly significant negative correlation (P<0.01) with serum GH level while it showed highly significant positive correlation (P<0.01) with plasma IGF-1 level.

Table (9): Pearson's correlations among the levels of hormones in the obese group

Parameters	Ghrelin	Leptin	Insulin	GH	IGF1
Ghrelin	1.000	-0.650**	-0.919**	0.965**	-0.920**
Leptin	-0.650**	1.000	0.603**	-0.568**	0.671**
Insulin	-0.919**	0.603**	1.000	-0.887	0.877**
GH	0.965**	-0.568**	-0.887**	1.000	-0.883**
IGF1	-0.920	0.671	0.877	-0.883	1.000

Data are expressed as coefficient of variation (r) values, asterisks indicate significant differences (**) $P<0.01$

Table (10) depicts Pearson's correlation between the levels of hormones and the tests of cognition in the control group. Only significant positive correlation ($P<0.05$) was found between plasma leptin level and TR.

Table (10): Pearson's correlation between the levels of hormones and cognition tests in the control group

Parameters	TR	TW	Digit span	coding	Recall	Classification
Ghrelin	0.111	0.080	-0.150	0.091	-0.124	0.070
Leptin	0.306*	0.060	0.047	0.204	0.276	0.165
Insulin	-0.014	0.127	-0.099	-0.118	-0.026	0.100
GH	-0.238	0.238	0.128	-0.228	-0.117	-0.130
IGF1	-0.054	0.054	0.009	0.192	0.243	0.151

Data are expressed as coefficient of variation (r) values, asterisks indicate significant differences (*) $P<0.05$

Table (11) illustrates Pearson's correlation between the levels of hormones and the cognitive tests in the obese group. Only significant negative correlation ($P<0.05$) was found between IGF-1 and coding scores.

Table (11): Pearson's correlation between the levels of hormones and cognition tests in the obese group

Parameters	TR	TW	Digit span	coding	Recall	Classification
Ghrelin	-0.130	0.147	-0.203	0.284	0.028	0.041
Leptin	0.092	-0.087	0.233	-0.192	-0.139	-0.119
Insulin	0.146	-0.156	0.194	-0.188	0.124	0.059
GH	-0.095	0.111	-0.172	0.280	-0.029	0.012
IGF1	0.131	-0.147	0.169	-0.294*	-0.053	-0.055

Data are expressed as coefficient of variation (r) values, asterisks indicate significant differences (*) $P<0.05$

4. Discussions

The present study revealed that serum ghrelin levels were highly significantly lower in the obese girls as compared with their controls. This fits well with results of Murphy *et al.* (2006). The down-regulation of ghrelin levels in obese subjects may be a consequence of elevated insulin or leptin, because fasting plasma ghrelin levels are inversely correlated with fasting plasma levels of insulin and leptin. This down-regulation may represent a physiological

adaptation to the positive energy balance associated with obesity (Tschöp *et al.*, 2001). However, Ikezaki *et al.* (2002) suggested that the down-regulation of ghrelin secretion may be a consequence of the high insulin resistance associated with visceral fat accumulation and elevated plasma plasminogen activator inhibitor 1 (PAI-1) concentrations, and not a consequence of total body (mainly subcutaneous) fat accumulation associated with elevated leptin concentrations. Our results demonstrated that, in obese subjects, serum ghrelin level showed highly significant inverse correlation with BMI and WC, and these findings are in accordance with those of Monti *et al.* (2006).

Our data showed that plasma leptin level was highly significantly increased in obese subjects as compared with the control. Similar results were recorded in obese children and adolescents (Druce and Bloom, 2006 and Venner *et al.*, 2006). This finding indicated that obesity is a state of leptin resistance. The resistance could be due to receptor defects, post-receptor defects or disruption of any of the integrative neuronal circuits necessary for leptin action (English and Wilding, 2006). In the current study, plasma leptin level was positively correlated with WC and FM%. These results are consistent with those of Aygun *et al.* (2005). Also, leptin levels in the obese group showed a significant positive correlation with BMI, and this coincides with results reported by Venner *et al.* (2006). Also, it has been found in adult men and women that leptin level was directly associated with BMI and WC (Monti *et al.*, 2006), and this supports our results.

Our results revealed that serum GH level is greatly diminished in obese girls and this result is in agreement with that of Riedel *et al.* (1995). Also, the recorded strong negative correlations between GH level and BMI, WC, HC and WC/Ht in obese girls in the present study are consistent with results of De Marinis *et al.* (2004). The decreased GH level in obese girls could be explained by the reduced GH pulsatile release and increased growth hormone clearance (Veldhuis *et al.*, 1991). However, Maccario *et al.* (2000) suggested that the decreased secretion of ghrelin, the endogenous ligand of the GHS-R, could be responsible for decreased level of circulating GH in obese individuals. Another explanation was reported as that in obese patients, high insulin level causes an increase in the hepatic GH receptor with IGF-1-preserved synthesis, decreases in IGFBP-1 and -2, and subsequently, a negative feedback of pituitary GH secretion is increased (Nam *et al.*, 1999). In fact, insulin can act directly at the pituitary level on GH secretion, through interaction with the IGF-1 receptor, thus incrementing the negative feedback of the pituitary GH secretion (Kratzsch *et al.*, 1997).

Total plasma IGF-1 level was significantly increased in the obese group as compared to the control. This result is in agreement with that of Bideci *et al.* (1997). Lukanova *et al.* (2002) reported that although, with increased adiposity, physiologic GH secretion is impaired and GH responses to all stimuli are decreased; insulin enhances GH-stimulated synthesis of IGF-1 through up-regulation of GH receptors. Reports have been mixed about the relationship between IGF-1 levels and body fat and/or insulin. The variable data in this concern may be attributed in part to differences in age, sex, degree of obesity or elevated insulin, and nutritional factors in study participants (Ahmed *et al.*, 2007). Our results showed a strong positive correlation between total IGF-1 and BMI ($P<0.01$) whereas others detected no correlation (Ahmed *et al.*, 2007). Total IGF-1 showed a positive correlation with insulin ($P<0.01$) and this coincides with the results of Nam *et al.* (1997). Lukanova *et al.* (2002) reported a nonlinear relation between IGF-1 and insulin in men but not women. Attia *et al.* (1998) reported that the differences in basal GH and IGF-1 levels observed in obese vs. lean subjects can be interpreted as expected compensatory adaptations to the insulin resistance and basal hyperinsulinemia that characterize the obese state. In fact, obese children grow normally although they have no evident or severely reduced GH secretion. This could be explained by elevated free IGF-1 levels or by postulating that basal GH levels in these children were enough to lead to normal growth (Ozata *et al.*, 2003).

In the current study, serum GH showed a significant positive correlation with ghrelin. Other studies reported the same and evidenced that the fasting-induced GH increase is preceded by an increase in ghrelin secretion (Shiiya *et al.*, 2002). As leptin has been shown to be an important mediator of the functioning of the somatotroph axis (Carro *et al.*, 2000), a logical deduction was that leptin may well be the signal to the human hypothalamus through which excess adipose mass inhibits GH secretion (Wauters *et al.*, 2000). This working hypothesis is coherent with the reports published on leptin values and GH secretion in some disease states and experimental models (Ghizzoni *et al.*, 2001) and with stepwise regression analysis indicating that leptin has a significant negative effect on GH secretion (Gill *et al.*, 1997). The results of Popovic *et al.* (2000) supported this hypothesis as they found that subjects respond to the GH stimulus in a negative correlation with the degree of adiposity, i.e. the more adipose tissue, the less GH released. Ozata *et al.* (2003) demonstrated the stimulated GH secretion in patients with human leptin deficiency and morbid obesity due to a missense mutation in the leptin gene. Our results revealed an inverse association between GH and leptin. This is in accord with results of other

studies (Kasa-Vubu *et al.*, 2002 and Misra *et al.*, 2008). In spite of these studies, it remains unclear whether high leptin levels cause a decrease in peak GH secretion in overweight girls or whether low GH concentration is associated with increased fat mass and, therefore, high leptin levels (Misra *et al.*, 2008).

In the present study, plasma insulin level increased significantly in the obese group as compared with the control group. This result is in accordance with that of Van Guilder *et al.* (2008) who mentioned that insulin resistance (IR) and compensatory hyperinsulinemia are the hallmarks of obesity, and individuals with upper body obesity show the greatest degree of insulin resistance and hyperinsulinemia. Several mechanisms could explain how obesity, especially visceral adiposity, leads to IR. For example, free fatty acids (FFA) released from fat deposits, especially visceral fat, can block the insulin signal pathways directly and thus interrupt insulin action, as well as insulin secretion (Zierath *et al.*, 1998). Moreover, increased amounts of FFA in the portal circulation may impair the metabolism and action of insulin and increase gluconeogenesis in the liver (Ferrannini *et al.*, 1983). In addition, adipocytokines such as TNF-α, adiponectin, resistin, and leptin, synthesized and secreted by adipocytes, have been found to be linked to IR associated with obesity (Yamauchi *et al.*, 2001). Our result showed a strong negative correlation between the levels of plasma insulin and serum GH levels in the obese girls. This result is supported by that of De Marinis *et al.* (2004). Consistent with data reported by other investigators (De Marinis *et al.*, 2004), there was highly significant positive correlation between plasma insulin level and plasma leptin level in the obese girls. Our results agree well with those of Bacha and Arslanian (2005) demonstrating an inverse relationship between fasting ghrelin level and fasting insulin in childhood obesity. Ghrelin secretion may be affected by adiposity through insulin and/or glucose metabolism (Soriano-Guillen *et al.*, 2004). Anderwald *et al.* (2003) demonstrated that intravenous administration of insulin induces a fall in ghrelin level. However, other authors disagree with these findings (Maffeis *et al.*, 2006). This decline in ghrelin concentration, in turn, is related to insulin sensitivity.

Our results demonstrated that the cognitive functions were adversely affected by obesity, the obese girls showed poorer functions in cognitive tests performed except for coding which was better in the obese group as compared with the control group. Our results are coherent with those of Campos *et al.* (1996) who found that obese children ages 8-13 years had significantly poorer performance on the Wechsler Intelligence Scale for Children (WISC) than their lean counterparts. Furthermore, Farr *et al.* (2008) reported that obesity is associated with decreased cognitive function. The mechanism (s) by which obesity results in cognitive impairment are uncertain. Postulated mechanisms include the effects of hyperglycemia, hyperinsulinemia, and vascular damage to the CNS (Morley, 2004). Hypertriglyceridemia is a hallmark of obesity. Increased level of triglycerides (TG) is likely one mechanism by which obesity can induce cognitive impairments through impairment of N-methyl-D-aspartate-mediated maintenance of hippocampal long-term synaptic potentiation (Farr *et al.*, 2008). Hypertriglyceridemia can also impair the transport of leptin across the blood-brain barrier, which may account in part for the peripheral leptin resistance seen in obesity and in starvation (Banks *et al.*, 2004). Leptin enhances cognition (Farr *et al.*, 2006). Thus, TG could impair cognition by preventing leptin from reaching the brain regions important for learning and memory. TG may also affect cognition through their ability to modify release of feeding peptides (Chang *et al.*, 2006), many of these peptides affect cognition through nitric oxide-dependent pathways (Diano *et al.*, 2006).

Using multiple stepwise regression analysis, when applying BMI as dependent variable, IGF-1 was the most significant independent determinant for obesity ($r^2 = 0.915$, $P > 0.01$) while when FM% was considered as the dependent variable, leptin was the most significant independent determinant for obesity ($r^2 = 0.087$, $P > 0.05$).

In conclusion, childhood obesity particularly in females represents a serious problem. Obesity could induce a disturbance in the levels of the vital hormones especially GH and IGF-1. In addition, obese status in girls at this young age is associated with worse educational achievements which reflect the impact of obesity on cognitive function and learning ability in these subjects. This may afford an aid in manipulating childhood obesity.

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1/3/2010