Insulin-like growth factor 1 and insulin-like growth factor binding protein-3 as predictive biomarkers of depression and migraine in obese women

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Introduction
Obesity and its comorbidity, depression and migraine, are highly prevalent conditions and public health problems of enormous scope that are responsible for the significant quality of life impairment and financial cost. Insulin-like growth factor-1 (IGF-1) and its main binding protein, insulin-like growth factor binding protein-3 (IGFBP-3) are related to metabolic diseases such as growth deficiency, obesity, cancer, neurological, and cardiovascular diseases. The objective of this study was to explore IGF-1 and IGFBP-3 in obesity-associated depression and migraine. Also, we aimed to evaluate the association of IGF-1 and IGFBP-3 with clinical features of depression and migraine.

Patients and methods
A cross-sectional controlled study included 50 healthy lean control group and 100 obese women who were subdivided into three subgroups: obese without depression and migraine (n=27), patients with depression (n=24), and patients with migraine (n=49). Clinical, neurological, and psychiatric evaluation of all patients was done. We measured IGF-1 and IGFBP-3 by commercial enzyme-linked immunosorbent assay.

Results
Our study showed a significantly lower level of IGF-1 and IGFBP-3 in obese women compared with lean ones. Even more importantly, obese women with depression as well as migraine had significantly lower IGF-1 and IGFBP-3 than those without depression and migraine. Interestingly, the lower levels of IGF-1 and IGFBP-3 in obese women with depression and migraine were significantly negatively correlated with depression score, BMI, and homeostasis model assessments of insulin resistance. Linear regression analysis test in obese patients showed that BMI and depression scores were independently correlated with serum IGF-1. However, BMI, fasting serum insulin, and depression scores were independently correlated with serum IGFBP-3.

Conclusions
Obese women with depression and migraine had significantly lower IGF-1 and IGFBP-3 than those without depression and migraine.

Keywords:
insulin-like growth factor-1, insulin-like growth factor binding protein-3 depression, migraine, obesity

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Introduction

Accumulating epidemiological evidence supports that obesity is a complex, multifactorial, and largely preventable disease [1], affecting, along with overweight, over a third of the world's population today [2]. If worldly trends continue, by 2030 an estimated 38% of the world's adult population will be overweight and another 20% will be obese. Obesity is dramatically growing in the Eastern Mediterranean region including Egypt. The prevalence of overweight and obesity, in this region, ranges from 74 to 86% among women and 69–77% among men [3].

Many recent studies have proposed that obesity and depression are associated [4]. Depression is an important public health concern as depression is the leading cause of years lived with disability [5]. Headache and obesity are prevalent and disabling disorders that are influenced by a variety of physiological, psychological, and behavioral mechanisms, many of which are affected by weight loss [6].

Insulin-like growth factor-1 (IGF-1) is a 70-amino acid polypeptide hormone with endocrine, paracrine, and autocrine effects, which shares structural homology (>60%) with IGF-2 and proinsulin [7]. IGF-1 availability is tightly regulated by insulin-like growth factor binding proteins (IGFBPs), which may act by increasing IGF-1 half-life, from minutes to hours (most commonly by forming a tertiary complex with acid-labile subunit and IGFBP3) [8].

Obesity is characterized by hyposomatotropinaemia [9]. IGF-1 is a primary determinant of neuroprotection from environmental enrichment [10]. Once in the brain, IGF-1 increases spontaneous hippocampal neuronal activity and improves hippocampus-dependent learning and memory test performance [11].

Compelling evidence suggests that depression, migraine, and obesity may be directly linked. Obesity is related to higher frequency and severity of headache attacks among individuals who have a migraine [12]. According to what has been discussed, it seems plausible that weight management strategies should be incorporated within a migraine treatment plan for patients who are obese [13]. Obesity is associated with concomitant or increased risk of nearly every chronic condition, from diabetes to dyslipidemia, to poor mental health. Its impact on the risk of stroke and cardiovascular disease, certain cancers, and osteoarthritis are evaluated in previous studies. To the best of our knowledge, there are no studies elucidating the role of IGF-1 and IGFBP-3 in obesity-associated depression and migraine. Therefore, we aimed to evaluate the association of IGF-1and IGFBP-3 with clinical features of depression and migraine.

Patients and methods

A cross-sectional, controlled study included 50 healthy lean control group; their BMI was less than 25 and 100 obese women of BMI more than 30 were subdivided into three subgroups: obese without depression and migraine (n=27), patients with depression (n=24), and patients with migraine (n=49). Obese women were recruited from the diabetes and endocrinology outpatient clinic of the Internal Medicine Department of Zagazig University. All patients were subjected to thorough history taking including job and qualification (years of school achievement), and full clinical assessment including blood pressure, waist circumference (a level midway between the lowest rib and the iliac crest), and hip circumference (widest diameter over the greater trochanters). Anthropometric variables including BMI was calculated as weight (kg)/height (m^2), waist–hip ratio (WHR)=waist circumference (cm)/hip circumference (cm). Neurological examination was done in the Neurology Department, Faculty of Medicine, Zagazig University. Migraine was diagnosed based on the criteria of the International Classification of Headache Disorders from the International Headache Society [14].

The psychiatric interview was carried out in the outpatient clinic of the Psychiatry Department of Zagazig University for the studied patients based on psychiatric diagnosis and social background. A structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) (severe combined immunodeficiency) was adopted. In addition, the psychometric assessment of depression and health-related quality of life was performed using an Arabic-adapted Beck Depression Inventory II (BDI-II) [15,16] and Short Form Scale-36, respectively [17]. BDI-II included 21 questions for which each answer is being scored on a scale value of 0–3. The cutoffs used were: 0–13: no or minimal depression, 14–19: mild depression, 20–28: moderate depression, and 29–63: severe depression [18].

Patients with cancer, stroke, or liver, kidney, thyroid, and cardiovascular or any active inflammatory diseases were excluded from this study. Obese patients with a positive family history of depression, migraine, and any type of severe or recurrent headache in first-degree relatives were excluded in migraine-free and depression-free obese patients. There was no concurrent minor infection reported during the study or during the month preceding the study.

Ethical consideration

Written informed consent was taken from all the participants after explaining details, benefits, and risks to them. The study design was approved by the Ethics Committee of Faculty of Medicine, Zagazig University.

Blood sampling

Blood samples were drawn from all patients after an overnight fast and were divided into two portions: 1 ml of whole blood was collected into evacuated tubes containing potassium oxalate and sodium fluoride (2 : 1) for fasting plasma glucose (FPG). Serum was separated immediately from the remaining part of the sample and stored at −20°C until analysis.

Biochemical analysis

We determined FPG levels using the glucose oxidase method (Spinreact, Girona, Spain). Total cholesterol, high-density lipoprotein cholesterol, and triglycerides levels were measured by routine enzymatic methods (Spinreact). The low-density lipoprotein cholesterol level was calculated using the Friedewald formula [19].

Immunochemical assays

Fasting serum insulin (FSI) concentrations were measured using a high-sensitivity linked immunosorbent assay (ELISA) kit provided by BioSource Europe S.A., Nivelles, Belgium). Homeostasis model assessments of insulin resistance (HOMA-IR) was calculated) was calculated as follows: FSI (mU/ml)×FPG (mg/dl)/405.

Measurement of serum insulin-like growth factor-1 and insulin-like growth factor binding protein-3 concentrations

Serum IGF-I and IGFBP-3 were measured using the following ELISA kits according to the manufacturer's instructions: IGF-1 ELISA kit (DRG International Inc., Springfield, New Jersey, USA), IGF-2 active nonextraction ELISA kit (Diagnostic Systems Laboratories Inc., Webster, Texas, USA), and IGFBP-3 Quantikine ELISA Kit (R&D Systems, Minneapolis, Minnesota, USA). Absorbance was read at 450 nm for the three kits in a microplate reader.

Statistical analysis

Data analyses were done with a statistical package for the social sciences software (version 21; SPSS Inc., Chicago, Illinois, USA). Data were expressed as the mean±SD. The relationships of IGF-1 and IGFBP-3 serum levels with clinical and laboratory parameters among obese patients in depression and migraine subgroups were tested with the Pearson correlation. Receiver operating characteristic analysis was performed to assess the diagnostic power of IGF-1 and IGFBP-3 serum levels. Linear regression analysis was done to detect the main predictors of serum IGF-1 and IGFBP-3 in the obese group. A P value of less than 0.05 was considered statistically significant.

Results

Clinical and laboratory characteristics of the studied groups

The clinical and laboratory characteristics of the studied women are summarized in Table 1. Obese patients had significantly higher values of systolic blood pressure, diastolic blood pressure, FPG, FSI, HOMA-IR, total cholesterol, low-density lipoprotein, and triglyceride levels compared with lean controls. Moreover, obesity indices and parameters, BMI and WHR, were significantly higher in obese women compared with lean patients. In contrast, obese patients had significantly lower levels of high-density lipoprotein than in healthy lean individuals ($P<0.001$).

Clinical and laboratory characteristics of obese groups

We found statistically significantly higher values of obesity indices, BMI, and WHR in obese women with depression ($n=24$) compared with obese women without depression ($n=27$) and obese with migraine ($n=49$) ($P<0.001$). Moreover, obese women with depression had statistically significantly higher values of systolic blood pressure, diastolic blood pressure, FSI, and HOMA-IR ($P<0.001$). Regarding obese women with migraine, they had statistically significantly higher values of obesity indices; BMI, and WHR ($P<0.001$) (Table 2).

Comparison of serum insulin-like growth factor-1 and insulin-like growth factor binding protein-3 in the studied groups

There were statistically significant differences of serum IGF-1 and IGFBP-3 in obese women with depression (288.1±51.19 and 2876.9±744), obese women with migraine (308.3±73.9 and 2951.3±647.3), obese women without depression and migraine (351.4 ±76.6 and 3765.4±830.6), and lean group (425.6 ±30.06 and 4371.5±416.6) (Fig. 1a and b, respectively).

Clinical and laboratory characteristics of obese women with depression

We classified our patients with depression into three subgroups according to the BDI-II score. We found statistically significantly higher values of obesity indices, BMI, and WHR in moderate and severe depression compared with mild depression ($P<0.001$). Moreover, obese women with severe depression had statistically significantly higher values of FPG, FSI, HOMA-IR, and depression scores ($P<0.001$). Interestingly, serum IGF-1 and IGFBP-3 were statistically significantly lower in obese women with severe and moderate depression compared with those with mild depression ($P<0.001$) (Table 3).

Clinical and laboratory characteristics of obese women with migraine

Among obese women with migraine ($n=49$), we found statistically significantly higher values of obesity indices, BMI, and WHR as well as FSI, HOMA-

Table 1 Clinical and laboratory characteristics of the studied groups

Variables	Control group (*n*=50) (mean±SD)	Obese group (*n*=100) (mean±SD)	*P* value
Age (years)	40.98±7.98	39.95±7.63	0.76
Menopausal status [*n* (%)]			
Premenopausal	31 (62)	56 (56)	0.557
Postmenopausal	19 (38)	44 (44)	
Marital status [*n* (%)]			
Single	17 (34)	36 (36)	0.381
Married	9 (18)	32 (32)	
Divorced	13 (26)	16 (16)	
Widow	11 (22)	16 (16)	
Employment status [*n* (%)]			
Active	22 (44)	56 (56)	0.242
Nonactive	28 (56)	44 (44)	
Systolic blood pressure (mmHg)	116.54±15.48	122.23±17.84	Ë 0.001*
Diastolic blood pressure (mmHg)	67.7±9.001	79.05±8.56	Ë 0.001*
Waist/hip ratio	0.79±0.076	1.03±0.11	Ë 0.001*
BMI (kg/m^2)	21.2±2.014	35.41±4.21	Ë 0.001*
TC (mg/dl)	161.76±18.87	197.56±8.87	Ë 0.001*
TG (mg/dl)	93.62±16.75	222.54±15.0	Ë 0.001*
LDL (mg/dl)	121.22±26.79	123.48±2.7	Ë 0.001*
HDL (mg/dl)	54.82±4.26	33.76±0.548	Ë 0.001*
FPG (mg/dl)	77.62±6.276	86.93±10.03	Ë 0.001*
FSI (μU/ml)	7.4±1.82	13.18±6.37	Ë 0.001*
HOMA-IR	1.57±0.40	5.7±4.14	Ë 0.001*

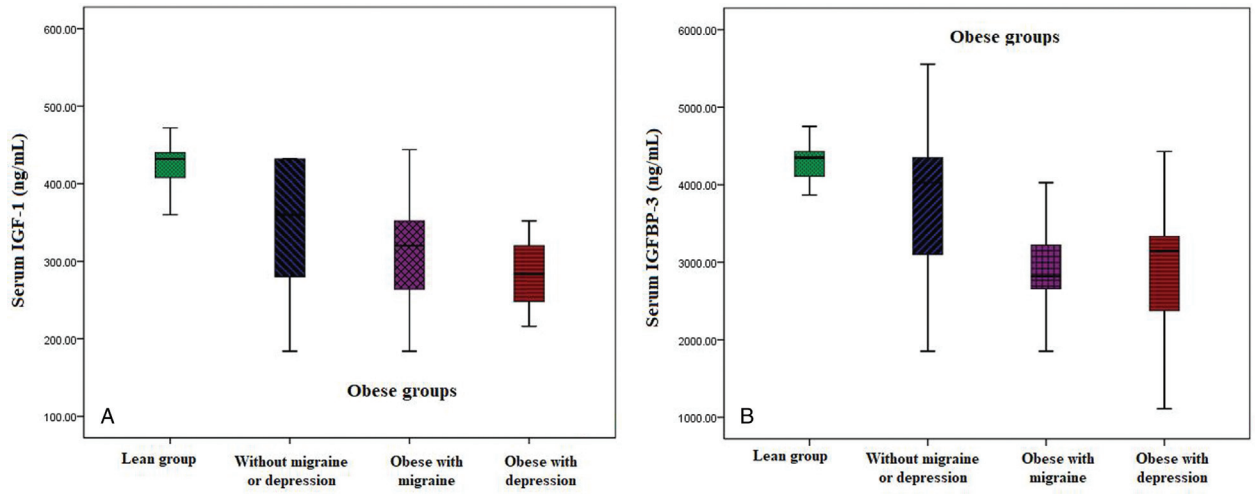
FPG, fasting plasma glucose; FSI, fasting serum insulin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessments of insulin resistance; LDL-C, low-density lipoprotein; TC, total cholesterol; TG, triglyceride. *$P<0.001$, when compared obese patients with the control group.

Table 2 Clinical and laboratory characteristics of obese groups

Variables	Without migraine or depression (*N*=27) (mean±SD)	Obese with migraine (*N*=49) (mean±SD)	Obese with depression (*N*=24) (mean±SD)
Menopausal status [*n* (%)]			
Premenopausal	17 (63)	28 (57)	11 (45)
Postmenopausal	10 (37)	21 (43)	13 (55)
Marital status [*n* (%)]			
Single	7 (25.9)	17 (33.7)	16 (32.6)
Married	8 (29.6)	19 (38.8)	5 (20.8)
Divorced	6 (22.2)	7 (14.3)	3 (12.5)
Widow	6 (22.2)	6 (12.2)	4 (16.7)
Employment status [*n* (%)]			
Active	13 (48.1)	28 (57.1)	15 (62.5)
Nonactive	14 (51.9)	21 (42.9)	9 (37.5)
Systolic blood pressure (mmHg)	122.1±11.7	115.5±11.1	131.5±24.1#
Diastolic blood pressure (mmHg)	73.7±9.82	74.51±7.2	80.05±8.9#
Waist/hip ratio	1.19±0.094	1.37±0.101*	1.52±0.118#
BMI (kg/m^2)	31.83±1.32	37.2±1.6*	42.87±1.9#
TC (mg/dl)	194.9±2.8	197.3±3.26	196.3±3.19
TG (mg/dl)	222±5.11	224.1±6.32	215.2±4.83
LDL (mg/dl)	123.6±2.6	123.1±2.9	122.9±2.85
HDL (mg/dl)	32.7±0.51	31.8±0.6	29.7±0.57
FPG (mg/dl)	85.96±9.4	88.49±8.08	88.8±9.3
FSI (μU/ml)	9.8±2.40	10.2±2.3	13.49±3.6#
HOMA-IR	4.2±1.2	4.7±1.6	5.4±1.4#

FPG, fasting plasma glucose; FSI, fasting serum insulin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessments of insulin resistance; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride. *$P<0.001$, when compared obese with migraine to obese women without migraine or depression. #$P<0.001$, when compared obese with depression to obese women without migraine or depression.

Figure 1



(a) Comparison of serum insulin-like growth factor-1 (IGF-1) (ng/ml) in the studied groups and (b) comparison of serum insulin-like growth factor binding protein-3 (IGFBP-3) (ng/ml) in the studied groups.

Table 3 Anthropometric, clinical, and laboratory characteristics of obese women with depression

Variables	Mild depression (*N*=10) (mean±SD)	Moderate depression (*N*=9) (mean±SD)	Severe depression (*N*=5) (mean±SD)
Systolic blood pressure (mmHg)	128.8±19.7	129.6±21.9	127.2±18.9
Diastolic blood pressure (mmHg)	79.0±7.57	82.10±7.51	81.41±7.5
Waist/hip ratio	0.99±0.096	1.03±0.087	1.13±0.10#
BMI (kg/m^2)	32.1±1.26	37.13±1.2*	41.55±1.3#
Total cholesterol (mg/dl)	198.4±2.6	197.5±2.9	197.2±3.1
Triglycerides (mg/dl)	224.2±4.8	225.5±5.1	224.1±5.2
LDL-C (mg/dl)	124.0±14.5	123.4±2.7	123.1±2.9
HDL-C (mg/dl)	29.6±5.51	29.7±5.52	29.8±0.72
FPG (mg/dl)	80.3±08.6	82.68±7.2	90.1±8.5#
FSI (μU/ml)	8.9±0.52	12.7±0.408*	14.1±0.528#
HOMA-IR	2.2±0.33	3.2±1.5	3.7±1.19#
Depression score	14.2±5.51	24.65±6.34	45.43±10.34
Antidepressant use			
No	2	1	1
TCA	7	6	3
SSRI	4	7	5
Other antidepressants	4	5	1
IGF-1 (ng/ml)	326.4±45.06	279.1±31.09*	227.2±9.12#
IGFBP-3 (ng/ml)	3372.7±404.1	2797.7±453.7*	2029.15±939.55#

FPG fasting plasma glucose; FSI, fasting serum insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessments of insulin resistance; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; LDL-C, low-density lipoprotein cholesterol; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. *P<0.001, when compared obese with moderate depression to obese women mild depression. #P<0.001, when compared obese with severe depression to obese women with mild depression.

IR, and accompanying symptoms, for example, nausea, vomiting, photophobia, and phonophobia in migraine with aura compared with migraine without aura (P<0.001). Interestingly, serum IGF-1 and IGFBP-3 were statistically significantly lower in migraine with aura compared with those without aura (P<0.001) (Table 4).

Correlations between serum insulin-like growth factor-1 and insulin-like growth factor binding protein-3 and other studied measures

Our results demonstrated significant negative correlations between serum IGF-1 and IGFBP-3 with BMI (Fig. 2a and Fig. 3a, respectively), HOMA-IR (Figs 2b and 3b, respectively), and

Table 4 Anthropometric, clinical, and laboratory characteristics of obese women with migraine

Variables	Migraine without aura (*N*=15) (mean±SD)	Migraine with aura (*N*=34) (mean±SD)	*P* value
Systolic blood pressure (mmHg)	119.1±11.7	118.5±11.1	0.905
Diastolic blood pressure (mmHg)	76.7±9.82	75.51±7.2	0.396
BMI (kg/m^2)	35.83±1.32	38.2±1.6	Ë 0.001*
Waist/hip ratio	1.299±0.09	1.57±0.101	Ë 0.001*
Total cholesterol (mg/dl)	178.9±2.8	180.3±3.26	0.431
Triglycerides (mg/dl)	95.3±5.11	99.4±6.32	0.083
LDL-C (mg/dl)	193.6±2.6	214.1±2.9	0.021
HDL-C (mg/dl)	33.7±0.51	37.8±0.6	0.084
FPG (mg/dl)	88.96±9.4	89.49±8.08	0.363
FSI (μU/ml)	6.8±1.40	10.8±3.5	Ë 0.001*
HOMA-IR	3.2±0.2	5.7±0.6	Ë 0.001*
Pain severity [*n* (%)]			
Low	3 (20)	6 (17.6)	0.689
Moderate	6 (40)	10 (29.4)	
severe	6 (40)	18 (52.9)	
Frequency of attacks [*n* (%)] (months)			
≤1	4 (26.7)	11 (32.4)	0.897
2–4	9 (60)	18 (52.9)	
≥5	2 (13.3)	5 (14.7)	
Unilateral localizations	8 (53.3)	19 (55.9)	0.556
Character of headache [*n* (%)]			
Pulsating	11 (73.3)	27 (79.4)	
Pressing/tightening	4 (26.7)	7 (20.6)	
Accompanying symptoms [*n* (%)]			
Nausea	5 (33.3)	14 (41.2)	0.044
Vomiting	5 (33.3)	5 (14.7)	
Photophobia	5 (33.3)	5 (14.7)	
Phonophobia	0 (0)	10 (29.4)	
Aggravation of headache by [*n* (%)]			
Physical activity	2 (13.3)	20 (58.8)	0.201
Menstruation	12 (80)	18 (52.9)	
Emotional stress	14 (93.3)	30 (88.2)	
Symptomatic treatment	46 (97.9)	14 (93.3)	0.754
Analgesics/NSAIDs	28 (59.6)	7 (46.7)	0.213
Triptans	1 (2.2)	1 (6.7)	0.067
Opioids [*n* (%)]			
Preventive treatment	16 (34.0)	4 (26.7)	0.184
β-Blockers	14 (29.8)	3 (20.0)	0.231
Calcium channel blockers	14 (29.8)	4 (26.7)	0.864
Anticonvulsant drugs	27 (57.4)	12 (80.0)	0.112
Antidepressive drugs (ng/ml)			
IGF-1	293.6±64.1	314.7±77.9	Ë 0.001*
IGFBP-3	2827.2±485.4	3006.01±706.7	Ë 0.001*

FPG, fasting plasma glucose; FSI, fasting serum insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessments of insulin resistance; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; LDL-C, low-density lipoprotein cholesterol. *P<0.05.

depression score (Figs 2c and 3c, respectively) ($P<0.001$).

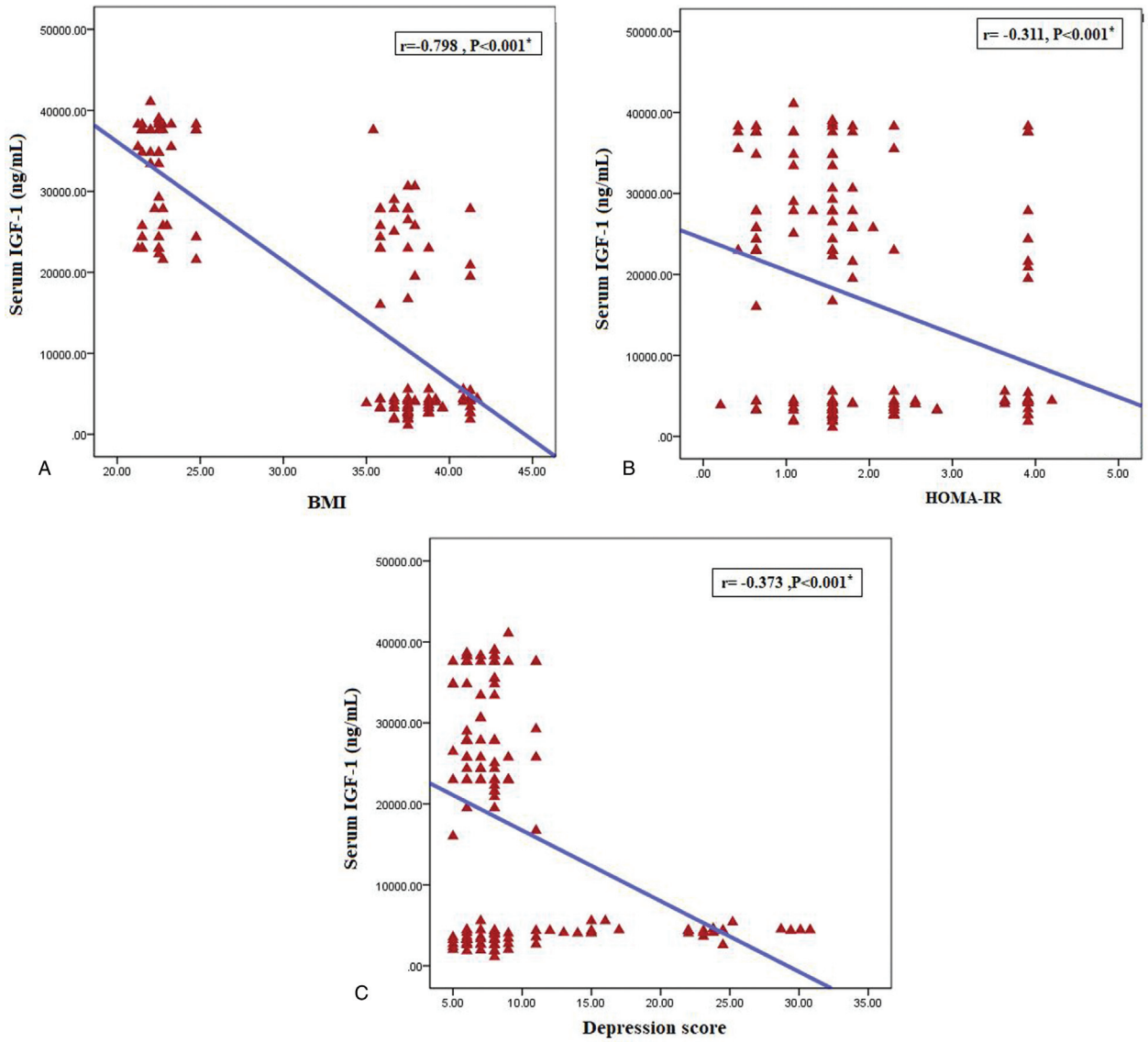
Linear regression analyses in obese patients to assess the main independent parameters associated with serum insulin-like growth factor-1 (ng/ml) and insulin-like growth factor binding protein-3 (ng/ml) levels

Linear regression analysis test showed that BMI and depression scores were independently correlated with serum IGF-1 ($P<0.001$) (Table 5). However, BMI, FSI, and depression scores were independently correlated with serum IGFBP-3 ($P<0.001$) (Table 5).

The accuracy of serum insulin-like growth factor-1 (ng/ml) and insulin-like growth factor binding protein-3 (ng/ml) for discriminating depression among obese women by receiver operating characteristic analysis

We further investigated the potential diagnostic value of serum IGF-1 and IGFBP-3 (ng/ml) by receiver operating characteristic curves presented in Fig. 4a. In

Figure 2



(a) Correlation between serum insulin-like growth factor-1 (IGF-1) (ng/ml) and BMI in obese groups, (b) correlation between serum IGF-1 (ng/ml) and homeostasis model assessments of insulin resistance (HOMA-IR) in obese groups, (c) correlation between serum IGF-1 (ng/ml) and depression score in obese groups.

obese patients, when we discriminate obese women with depression among obese women, the cutoff values of serum IGF-1 and IGFBP-3 were 356.1 and 3463.22 and the area under the curve was 0.765 [95% confidence interval (CI)=0.676–0.853] and 0.737 (95% CI=0.645–0.829), respectively. In addition, the sensitivities and the specificities of IGF-1 and IGFBP-3 were 95.8 and 95.4% and 91.7 and 61.1%, respectively.

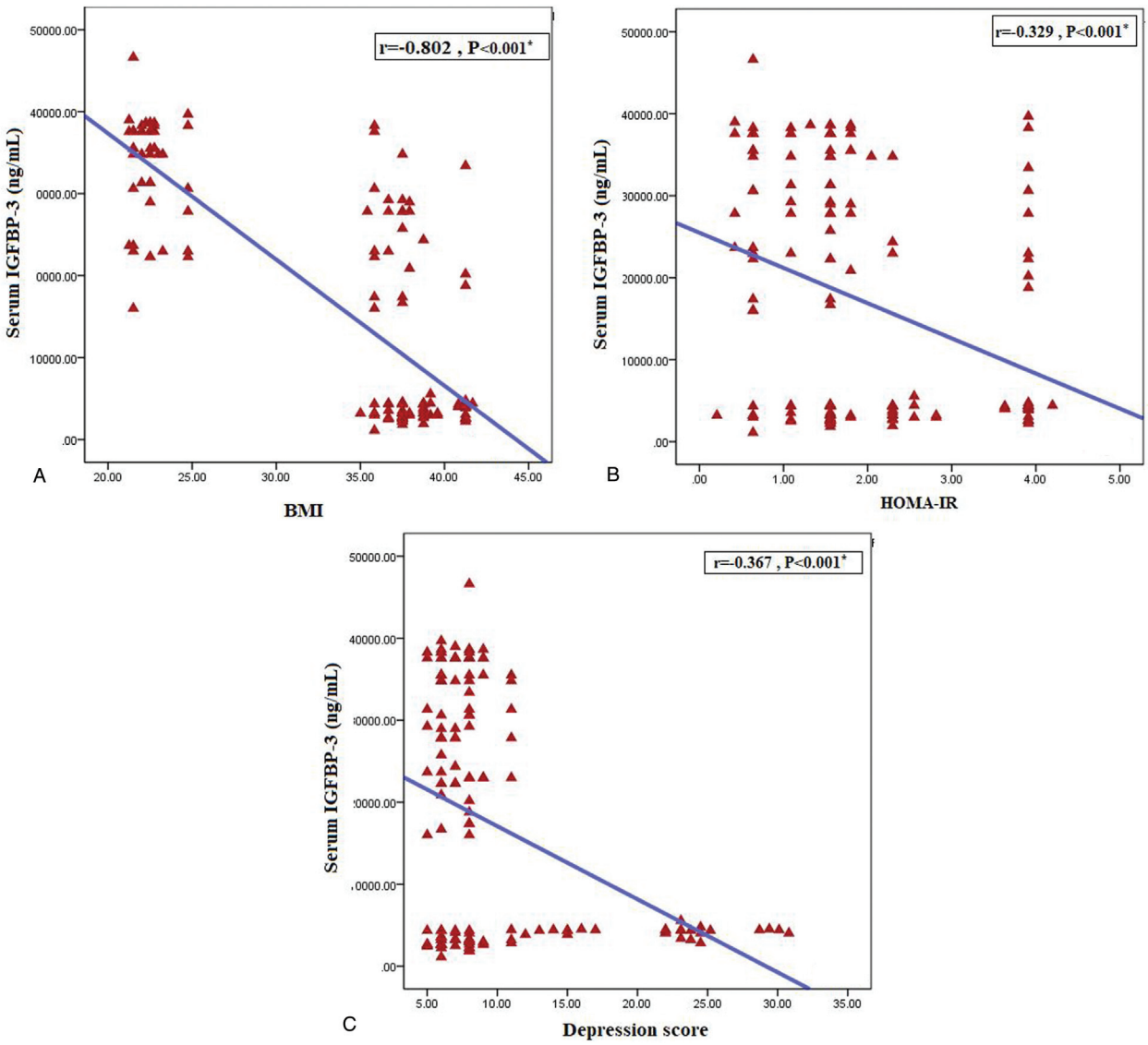
The accuracy of serum insulin-like growth factor-1 (ng/ml) and insulin-like growth factor binding protein-3 (ng/ml) for discriminating obese women with migraine from obese women without migraine by receiver operating characteristic analysis

In obese patients, when we discriminate obese women with migraine from obese women without migraine, the cutoff values of serum IGF-1 and IGFBP-3 (ng/ml) were 404.1 and 4067.27 and the area under the curve was 0.795 (95% CI=0.706–0.885) and 0.890 (95% CI=0.828–0.952), respectively. In addition, the sensitivities and specificities of IGF-1 and IGFBP-3 were 85.7 and 65.9% and 93.9 and 97.1%, respectively.

Discussion

Obesity has become a major contributor to the global burden of chronic disease and disability. It is a complex condition with serious social and psychological dimensions, affecting virtually all ages and socioeconomic groups [20]. Depression and obesity are common, with an estimated 350 and 500 million people globally [20,21]. Several lines of evidence

Figure 3



(a) Correlation between serum insulin-like growth factor binding protein-3 (IGFBP-3) (ng/ml) and BMI in obese groups, (b) correlation between serum IGFBP-3 (ng/ml) and homeostasis model assessments of insulin resistance (HOMA-IR) in obese groups, (c) correlation between serum IGFBP-3 (ng/ml) and depression score in obese groups.

indicate the reciprocal relationship between depression and obesity. Compelling evidence suggests that depression and obesity are both associated with social stigma, low self-esteem, and chronic health conditions [22].

Headache and obesity are prevalent and disabling disorders that are influenced by a variety of physiological, psychological, and behavioral mechanisms, many of which are affected by weight loss [6]. It is not uncommon for migraineur patients to be obese. Recently, attention has focused on the potential relationship between overweight and frequency and severity of headache attacks [23,24] and some evidence for this relationship has been demonstrated [25,26].

IGF-1 is a primary determinant of neuroprotection from environmental enrichment [10] Once in the brain, IGF-1 increases spontaneous hippocampal neuronal activity and improves hippocampus-dependent learning and memory test performance [11]. Once migraine, depression, and obesity co-occur, the adverse health and social consequences are significant. Therefore, we aimed to assess the prevalence of depression and migraine among obese women and to evaluate the association of IGF-1and IGFBP-3 with clinical features of depression and migraine.

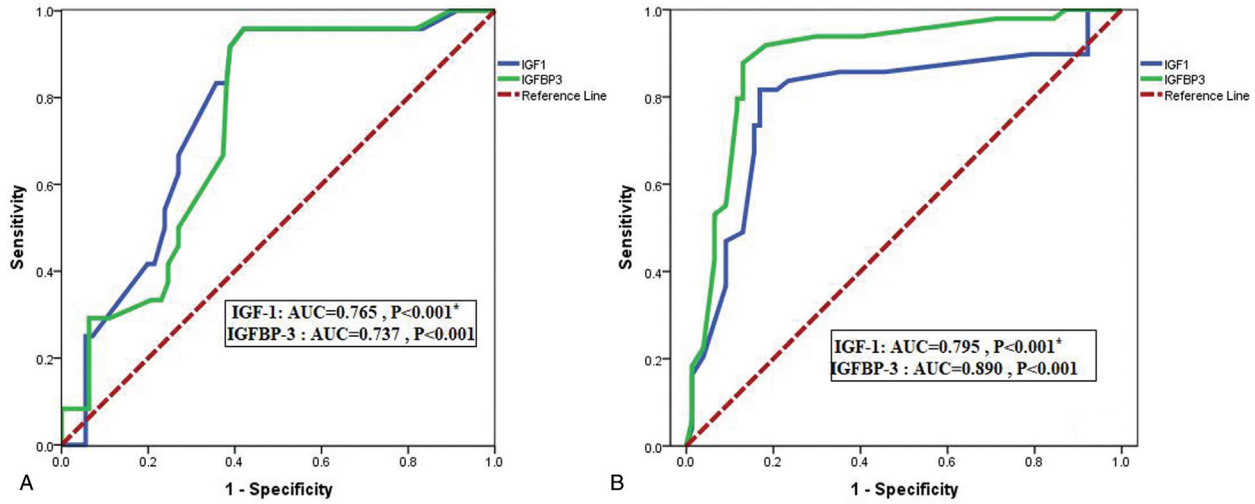
The results presented herein are innovative as this study performs a robust estimation of the prevalence of depression and migraine among obese women.

Table 5 Linear regression analyses to test the influence of the main independent variables against serum insulin-like growth factor-1 (ng/ml) and insulin-like growth factor binding protein-3 (ng/ml) levels (dependent variable) in obese patients

Model	Unstandardized coefficients *B*	SE	Standardized coefficients *β*	*t*	*P* value	Lower Bound	95% CI Upper Bound
IGF-1							
Constant	7.089	2.963	–	2.393	0.018	12.940	1.239
DBP	0.001	0.002	0.048	0.747	0.456	0.002	0.004
BMI	0.028	0.004	0.551	6.946	Ë 0.001*	0.020	0.036
Depression score	0.012	0.002	0.466	4.815	Ë 0.001*	0.007	0.016
FPG	0.001	0.001	0.061	1.007	0.315	0.000	0.004
HDL	0.083	0.051	0.211	1.634	0.104	0.017	0.184
IGFBP-3							
Constant	31.56	13.951	–	2.263	0.025	59.122	4.017
SBP	0.007	0.004	0.103	1.837	0.068	0.001	0.014
BMI	0.189	0.019	0.702	9.841	Ë 0.001*	0.151	0.227
Depression score	0.055	0.011	0.425	4.884	Ë 0.001*	0.033	0.078
FSI	4.43	0.895	0.430	4.950	Ë 0.001*	6.200	2.665

CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FSI, fasting serum insulin; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; SBP, systolic blood pressure. *P<0.05.

Figure 4



(a) Receiver operating characteristic (ROC) of serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) (ng/ml) for discriminating obese women with depression from obese women without depression, (b) ROC of serum IGF-1 and IGFBP-3 (ng/ml) for discriminating obese women with migraine from obese women without migraine. AUC, area under the curve.

According to our cross-sectional study, about 24% had depression.

Similar to our result, a study conducted by Carey *et al.* [27] observed that the prevalence of depression was 23% among obese participants.

In this report, we have demonstrated the reciprocal relationship between depression and obesity. In a study conducted in Saudi Arabia to assess the correlation between obesity and depression among male students of King Khalid University it has been found that the prevalence of overweight and obesity is considerably high and suggested that obesity is associated with depression, anxiety, and stress [28].

Similar findings were observed in the Egyptian study by Kamel *et al.* [29]. They detected that the prevalence of obesity was higher in female patients (79.31%) than in male patients (20.69%). Moreover, the incidence of depressive disorders was higher in female patients (47.83%) than male patients [29].

Regarding migraine, our results have shown that 49% of obese women had migraine. In agreement with our results, a study conducted by Prieto Peres *et al.* [30] found that obese patients were three times as likely as age-matched normal-weight controls to have a migraine, even more importantly, about 75% of obese patients had lifetime headache diagnosis as compared with 42% of the controls.

The interesting finding of Horev *et al.* [31] found that 63% of 27 patients with obesity reported episodic headache and 48% fulfilled migraine criteria. The higher prevalence of episodic headache and migraine compared with our results that were observed in this study could be due to the differences in weight in studied cases as Horev *et al.* [31] studied morbidly obese women, while our patients were moderately obese as the BMI was 35.4.

The study by Afshinmajd *et al.* [32] showed that obesity has a direct influence on the treatment of migraine headaches. The treatment of migraine had a direct association with BMI increments. In contrast, a study by Bigal *et al.* [23] showed that obesity was not associated with an increased prevalence of migraine but was related to headache attack frequency [33,34]. The mechanism by which obesity affects migraine or its treatment is unknown but the mechanism that influence body weight may simultaneously influence migraine.

The results presented here are innovative, as this study was the first Egyptian study that investigated the possible association of serum IGF-1 and IGFBP-3 with obesity, depression, and migraine. In this study, we found a significantly lower level of IGF-1 and IGFBP-3 in obese women compared with lean women.

In the study conducted by Nam *et al.* [35], it has been found that total IGF-1 and IGFBP-3 concentrations were not significantly different between the obese and control groups; even more importantly, they found that free IGF-1 concentrations were higher in obese patients than in normal controls. The explanation of their finding could be due to overnutrition and chronic hyperinsulinemia in obesity may alter this regulated growth response by insulin stimulation of IGF-1 production and suppression of hepatic IGFBP-1 and IGFBP-2 production, which may inhibit IGF-1 bioactivity [35].

Our results have shown significantly lower levels of IGF-1 and IGFBP-3 in obese women with depression and migraine compared with obese women without depression and migraine. Interestingly, lower levels of IGF-1 and IGFBP-3 in obese women with depression and migraine were significantly negatively correlated with depression score, BMI, and HOMA-IR. Even more importantly, the linear regression analysis test showed that BMI and depression scores were independently correlated with serum IGF-1. However, BMI, FSI, and depression scores were independently correlated with serum IGFBP-3.

The results of the study by Sievers *et al.* [36] observed lower levels of peripheral IGF-1 in depressive disorders. In contrast, a study by Bot *et al.* [37] detected higher levels of plasma IGF-1 in depression. The elevation of peripheral IGF-1 concentrations may be explained by the decreased cerebral bioavailability of the neurotrophin due to decreased sensitivity of IGF-1 receptors under the neuroinflammatory stress [38].

Controversial findings of IGF-1 levels in patients with depression compared with controls could be explained by variations of sex hormones or fluctuations of growth hormone and IGF-1-binding protein [39]. In addition, Rosso *et al.* found no correlations between baseline IGF-1 levels and clinical features of depression.

Conclusion

A lower level of IGF-1 and IGFBP-3 was found in obese women compared with lean ones. Even more importantly, obese women with depression as well as migraine had significantly lower IGF-1 and IGFBP-3 than those without depression and migraine. Early prediction of depression and migraine among obese patients decreases morbidity. Thus, future multicenter studies are needed to validate our findings.

Limitations

Some limitations should be considered. First, the sex of the study population was only females. Second, the small sample size of the study and further studies with a larger sample size should be performed in the future to validate our results. Third, the study was of the cross-sectional type that does not allow us to distinguish between causal mechanisms or examine how they might differ across sociodemographic variables.

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Conflicts of interest

There are no conflicts of interest.

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