Association of serum visfatin and its mRNA expression levels with cognitive function and idiopathic intracranial hypertension in obese Egyptian women

Nearmeen M. Rashad[a], Hanan M. Sabry[b], Amira A. Fouad[c], Samir A. Afifi[a], Maha A. Fathy[d], Amira M. El-Helaly[e]

Departments of [a]Internal Medicine, [b]Neurology, [c]Psychiatry, [d]Physiology, [e]Clinical Pathology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Correspondence to Nearmeen M. Rashad, MD, Department of Internal Medicine, Faculty of Medicine, Zagazig University, 44519, Zagazig, Egypt.
Tel: +20 122 424 8642;
e-mail: nrashad78@yahoo.com

Received: 3 October 2019
Revised: 13 October 2019
Accepted: 3 December 2019
Published: 18 August 2020

The Egyptian Journal of Internal Medicine
2019, 31:763–773

Background
An epidemic of obesity has spread across the globe. Obesity has numerous comorbidities, including airway disease, insulin resistance, type 2 diabetes, cardiovascular disease, atherosclerosis, degenerative neurological disease, cognitive dysfunction, and cancer. Inflammatory cytokine is suggested to play a role in obesity and its complications. The current study aimed to estimate the expression and serum visfatin concentrations in obese Egyptian women. Moreover, we aimed to evaluate the possible association of visfatin gene expression and its serum levels with idiopathic intracranial hypertension (IIH) and cognitive dysfunction

Participants and methods
This cross-sectional study enrolled 60 obese women and 40 lean healthy women as controls. Obese women were classified according to grades of obesity into three groups. All participants underwent full clinical, neurological, and psychiatric examination. IIH group included patients with intracranial pressure greater than 25 cmH_2O (opening pressure measured during lumber puncture in lateral decubitus position). Cognitive function was evaluated by using Montreal Cognitive Assessment scale (MoCA), Arabic version. Estimation of visfatin expression levels was determined by real-time PCR, and serum visfatin concentrations were measured using enzyme-linked immunosorbent assay.

Results
Our results revealed that obese women had higher values of visfatin expression (1.44±0.29) and serum levels (124.1±) compared with lean women (1.01±0.3 and 46.1±33.8, respectively). The visfatin expression and serum levels were significantly positively correlated with obesity indices, metabolic risks, MoCA, cerebrospinal fluid opening pressure, and cognitive dysfunction. Linear regression test showed that BMI, cerebrospinal fluid opening pressure, and MoCA were the main predictors of both serum and expression levels of visfatin in obese women. The receiver operating characteristic curve analysis revealed that the power of serum visfatin levels was higher than visfatin expression in differentiating obese women from lean ones.

Conclusion
There was a strong independent association between both higher visfatin expression and serum levels and obesity indices, metabolic risks, IIH, and cognitive dysfunction in obese Egyptian women.

Keywords:
cognitive dysfunction, idiopathic intracranial hypertension, obesity, visfatin gene expression

Egypt J Intern Med 31:763–773

1110-7782

Introduction

The prevalence of obesity is rapidly increasing worldwide. The WHO current estimates of obesity as a global health crisis are that 500 million adults are obese and 1.5 billion adults are overweight, the majority of which are in developing countries [1]. The prevalence of obesity in Egypt has increased at an alarming rate during the past three decades, affecting 22% of adult males and 48% of adult females [2]. It is associated with several comorbidities, including hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, stroke, osteoarthritis, sleep apnea, peripheral neuropathy, as well as some types of cancers [3–5].

A preponderance of evidence confirmed that idiopathic intracranial hypertension (IIH) is a syndrome of raised

intracranial pressure, with normal cerebrospinal fluid (CSF) composition and normal brain parenchyma, without any ventriculomegaly or mass lesion. Intriguing reports have investigated its association with obesity. Headache is the most common symptom associated with IIH [6,7], and the most concerning symptom is vision loss [8]. Papilledema usually accompanies headache, both occurring in almost 90% of patients. The headache of IIH is mainly managed using medications that decrease ICP [9]. Other complications of IIH primarily include diplopia and tinnitus [6,10].

It has been postulated that cognitive function is a construct that represents an individual's ability to attain information and thus knowledge with constant application of memory, attention, and language skills [11]. A growing body of evidence has corroborated that obesity may influence cognitive function. There are several hypotheses that explain the pathophysiological changes of cognitive dysfunction in obesity, including vascular changes, insulin resistance, inflammation, reduced body fitness, especially cardiovascular, and so on [12,13]. Evidence suggests that the effect of obesity on cognitive function is not straightforward, rather obesity tends to affect the cognitive function of different people in different ways, specifically depending upon their age group [14,15].

Recently published studies highlighted the value of adipocytokines in regulating metabolism and insulin resistance. Visfatin is a 52 kDa cytokine expressed in lymphocytes that bind to the insulin receptor affecting insulin resistance, and it corresponds to a protein identified previously as a pre-B-cell colony-enhancing factor [16].

Numerous publications have reported various effects and correlations of visfatin with different medical conditions. In this way, the increase in visfatin level can be observed in atherosclerosis, endothelial dysfunctions, and renal insufficiency [17].

This adipokine has physiological influences on the control of glucose homeostasis through its insulin-mimetic action; however, its association with obesity is not established [18]. Another function of visfatin is the regulation of inflammatory and immunomodulating processes [16]. It was demonstrated that serum levels of visfatin were independently correlated with C-reactive protein and interleukin-6 in obese patients [19]

Participants and method

Participants

This case–control study included sixty obese patients (BMI >30) recruited from Outpatient Clinics of the Endocrinology Unit of Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt, and 40 healthy lean women (BMI <25) matched with obese cases regarding age. Obese women were then stratified according to their BMI into one of three subgroups: group I (BMI=30–34.9 kg/m^2), group II (BMI=35–39.9 kg/m^2), and group III (BMI $> 40\ kg/m^2$).

The enrolled patients were evaluated by history talking; clinical symptoms, with special emphasis on duration of symptoms, presenting symptoms (headache type and site, nausea, vomiting), and ocular symptoms, such as transient visual obscuration, double-vision, and visual field defects); and neurological examination, which was done in Neurological Department, Faculty of Medicine, Zagazig University, Egypt. IIH patient group included patients with intracranial pressure greater than 25 cmH_2O measured in lateral decubitus position, normal CSF composition, and absence of hydrocephalus or mass in brain imaging [20]. Ophthalmological assessment including Frisen classification for papilledema, visual acuity, visual field, and visual evoked potentials was performed for the patients.

Psychiatric assessment was done in the Neurological Department, Faculty of Medicine, Zagazig University, Egypt. We evaluated cognitive function by using Montreal Cognitive Assessment scale (MoCA), Arabic version [21]. It is a 30-point test, in which a score less than 26 points indicates a mild cognitive impairment. It assesses visual-spatial abilities, multiple aspects of executive functions, language, short-term memory, attention, concentration, working memory, and a serial subtraction task (three points). Orientation and place are assessed at the end of the test [22].

Lumbar puncture was performed under local anesthesia using a 20 G needle that was inserted under complete aseptic precautions in L4–L5 vertebral space. The opening pressure was measured. Written informed consent was taken from all of the participants after explaining details and benefits as well as risks to them. The Ethical Committee of the Faculty of Medicine, Zagazig University, approved this study. We excluded patients with features of secondary IIH, such as cerebral venous sinus thrombosis. In addition, we

excluded patients having major language disturbance, patients with severe physical, patients with visual or auditory impairment affecting their ability to complete testing, patients with a history of alcohol intake or any substance abuse, patients having any other medical or metabolic illness known to impair cognition, patients with current or previous major psychiatric disorder and/or current use of drugs as anxiolytic, neuroleptic, or sedative, as well as pregnant women, and patients with known comorbidities as hypertension or diabetes mellitus.

The accurate and precise values of the body composition parameters were estimated from the DEXA scan of the total body. They included fat mass (FM) and fat-free mass (FFM). Additionally, the FM index (FMI) [FM/square height (kg/m^2)] and FFM index (FFMI) [FFM/square height (kg/m^2)] were calculated. Neuroimaging studies including MRI brain (sagittal, coronal, and axial cuts in all sequences) and magnetic resonance venography using 1.5-T Philips Intera scanner (Philips Healthcare, Amsterdam, the Netherlands) were done to exclude hydrocephalus, mass lesions, or other pathologies.

Sampling of blood

The blood samples of all study's participants were drawn after an overnight fast and divided into three portions: 1 ml of whole blood was collected into EDTA tubes, for RNA extraction and HbA1c; 1 ml of blood was collected into potassium oxalate and sodium fluoride-containing tubes for fasting plasma glucose (FPG). Sera were separated from the remaining sample part and stored at −20°C until analysis.

Biochemical analysis

We determined FBG and 2 h plasma glucose levels using the glucose oxidase method (Spinreact, Girona, Spain). Total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were measured by routine enzymatic methods (Spinreact, Girona, Spain). The low-density lipoprotein cholesterol level was calculated using the Friedewald formula [23].

Measurement of visfatin

Plasma visfatin was measured using an enzyme-linked immunosorbent assay kit (USCN Life Science Inc., Wuhan, China), with a lower limit of sensitivity of 0.78 ng/ml (range: 3.12–200 ng/ml). The interassay and intra-assay coefficients of variation were less than 14 and less than 5%, respectively.

RNA extraction, cDNA synthesis, and real-time PCR for visfatin mRNA gene expression

Ficoll gradient centrifugation was conducted to obtain PBMCs from the whole blood. Heparinized blood was mixed with 20-ml PBS, layered onto Ficoll-Hypaque (TBD Science, Tianjin, China) and centrifuged for 20 min at 2500 rpm (TDL-40B low-speed horizontal centrifuge; ANTING Scientific Instrument Plant, Shanghai, China). The interface containing the mononuclear cells was collected and washed three times using PBS. The cells were resuspended at 1×106 cells/ml in RPMI 1640 medium (1% penicillin/streptomycin and 10% new-born calf serum) and seeded into 6-well plates at 37°C in a 5% CO_2 humidified incubator. After 12 h, the nonadherent cells were removed, and a number of the remaining PBMCs were cultured in RPMI 1640 for 96 h to obtain RNA. Additional PBMCs were cultured in RPMI 1640 with 100 nmol/l phorbol-12-myristate-13-acetate (Sigma-Aldrich, St. Louis, Missouri, USA) for 48 h to obtain monocyte-derived macrophages, and the RNA was isolated after 96 h. qPCR. Total RNA was isolated from the cells using TRIzol reagent (Invitrogen Life Technologies, Carlsbad, California, USA), with 7 μl of total RNA undergoing reverse transcription in a 20 μl volume oligo dT12–18 Primer, according to the manufacturer's instructions for the SuperScript III First-Strand cDNA Synthesis System (Invitrogen Life Technologies).

A reverse-transcribed reaction (1 μl aliquot) served as the template in a 20 μl PCR, which contained 0.2 μl per primer, 9.6 μl ddH_2O, and 9 μl 2.5X RealMaster SYBR Green I mix (Tiangen Biotech, Beijing, China) for visfatin and 0.4 μl per primer, 9.2 μl ddH_2O and 9 μl 2.5X RealMaster SYBR Green I mix for β-actin. qPCR analysis was performed in a fluorescent temperature cycler (Mastercycler ep real lex; Eppendorf, Hamburg, Germany). Initial denaturation was conducted at 95°C for 2 min, and the subsequent reactions were cycled 35 times using the following parameters to enable visfatin detection: denaturation at 95°C for 15 s, primer annealing at 62.7°C for 15 s, and primer extension at 68°C for 20 s. The human visfatin oligonucleotide primers were as follows: sense, 5′-AAGAGA CTGCTGGCATAG GA-3′, and antisense, 5′-ACCACAGATACAG GCACTGA-3′. mRNA detection of human β-actin was conducted as follows: denaturation at 95°C for 2 min, 40 cycles at 95°C for 15 s, primer annealing at 60°C for 15 s, and extension at 68°C for 20 s. The human β-actin oligonucleotide primers were as follows: sense, 5′-TGACGTGGACATC CGCAAAG-3′, and antisense, 5′-CTGGAAGGTG

GACAGCGAGG-3′. The lengths of the qPCR products for visfatin and β-actin were 228 and 205 bp, respectively. Gel electrophoresis and melting curve analyses were applied to confirm the amplification specificity of the qPCR products from each primer pair. Standard curve methods were used to obtain the concentration of the samples, and the relative visfatin mRNA levels were standardized against those of β-actin.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 22.0; SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean±SD and were analyzed using Student's *t*-test. A comparison of several means was done by one-way analysis of variance, followed by the least significance difference test for multiple comparisons between groups. Pearson's correlation coefficient was used to assess the association of visfatin expression and serum levels with studied parameters in obese women. We explored by linear regression analysis the main independent variables of visfatin expression and serum levels among the obese group. Receiver operating characteristic (ROC) analysis was performed to assess the potential diagnostic accuracy of visfatin expression and serum levels, the area under the curve (AUC), and the cutoff values. We considered *P* to be significant at less than 0.05 with a 95% confidence interval (CI).

Results

Clinical, anthropometric, and biochemical characteristics of the studied groups are summarized

In obese patients, there were significantly higher values of systolic blood pressure, diastolic blood pressure, FPG, triglycerides, total cholesterol, LDL cholesterol, MoCA, and CSF opening pressure as compared with controls (Table 1). Moreover, BMI, waist/hip ratio, FFMI, and FMI were significantly higher in obese patients than the control group. On the contrary, HDL was significantly lower in the obese groups as compared with the control group ($P<0.001$). Regarding the clinical characteristics associated with IIH, there was a higher prevalence of headache (91%), transient visual obstruction (62%), back pain (63%), pulsatile tinnitus (58%), dizziness (54%), photophobia (44%), neck pain (64%), visual loss (22%), nocturia (23%), cognitive (66%), radicular pain (19 %), and diplopia (21%) in obese women (Fig. 1).

Clinical, anthropometric, and biochemical characteristics of obese groups

Among obese groups, group II had significantly higher values of triglycerides, total cholesterol, LDL cholesterol, MoCA, CSF opening pressure, BMI, waist/hip ratio, FFMI, and FMI as compared with group I. Regarding group III, there were significantly higher values of BMI, waist/hip ratio, FFMI, FMI, triglycerides, total cholesterol, and LDL cholesterol, compared with group I ($P<0.001$) (Table 2).

Comparison of visfatin serum (ng/ml) and gene expression levels in the studied groups

There were significant differences among the studied groups regarding serum visfatin, as higher level was detected in group III (126.3±7.8) compared with group II (104.2±17.2), group I (94.1±5.6), and the control group (23.7±3.1) ($P<0.001$*), as shown in Fig. 2.

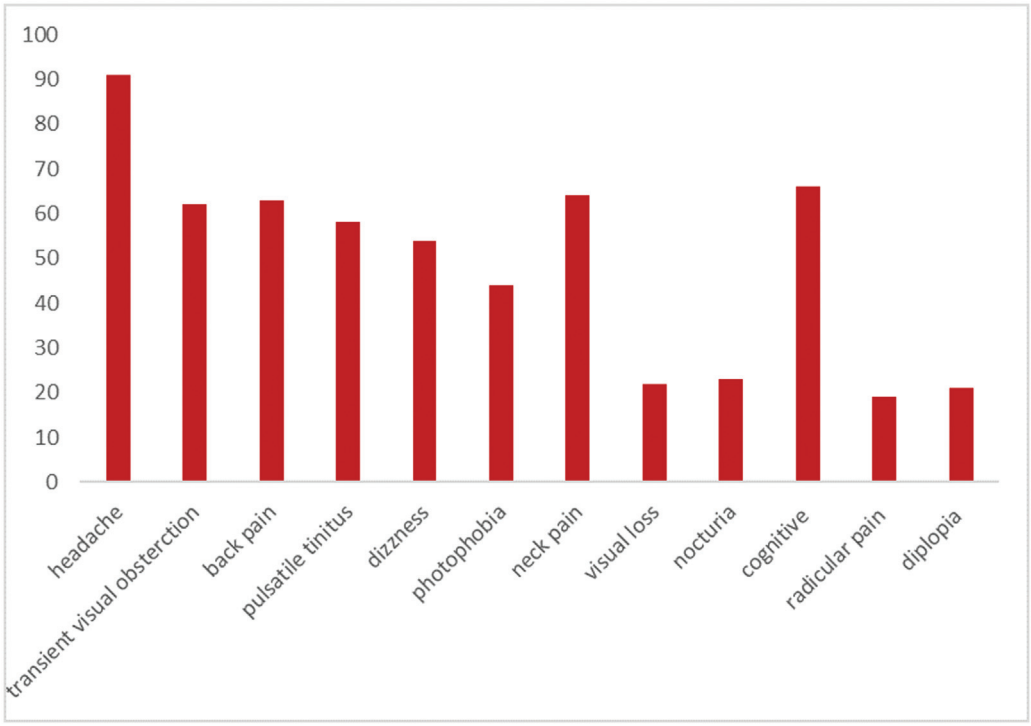
Regarding visfatin gene expression levels, there were higher levels in group III (1.48±1.17) compared with the group II (1.15±18), group I (1.04±0.06), and the control group (0.98±0.13) ($P<0.001$*), as shown in Fig. 3.

Table 1 Clinical, anthropometric, and laboratory characteristics of all studied participants

	Control group (mean±SD) (*n*=40)	Obese group (mean±SD) (*n*=60)	*P*
Age (years)	44.88±6.53	43.74±7.24	0.209
Systolic blood pressure (mmHg)	126.2±20.68	140.5±17.14	<0.001*
Diastolic blood pressure (mmHg)	76.26±8.17	79.8±7.28	<0.001*
Waist/hip ratio	0.85±0.09	1.49±0.519	<0.001*
BMI (kg/m^2)	22.96±3.62	33.03±4.52	<0.001*
FMI (kg/m^2)	3.76±0.66	8.63± 6.244	<0.001*
FFMI (kg/m^2)	19.0±1.160	24.4±3.286	<0.001*
Total cholesterol (mg/dl)	164.36±55.67	202.07±60.37	<0.001*
Triglycerides (mg/dl)	118.5±46.79	213.6±87.8	<0.001*
LDL cholesterol (mg/dl)	105.16±44.35	140.2±43.28	<0.001*
HDL cholesterol (mg/dl)	54.24±4.1	35.5±9.078	<0.001*
FPG (mg/dl)	90.9±6.447	130.6±36.92	<0.001*
MoCA	22.7±2.41	26.4±2.31	<0.001*
CSF opening pressure (mm H_2O)	228.3±14.14	249.3±60.14	<0.001*

CSF, cerebrospinal fluid; FFMI, fat free mass index; FMI, fat mass index; MoCA, Montreal Cognitive Assessment. *$P<0.05$, significant.

Figure 1



The prevalence of clinical characteristics associated with idiopathic intracranial hypertension.

Table 2 Clinical, anthropometric, and laboratory characteristics in obese patients

	Group I (mean±SD) (*n*=11)	Group II (mean±SD) (*n*=20)	Group III (mean±SD) (*n*=29)	P_1	P_2
Age (years)	43.02+8.135	43.76+5.986	44.62+7.85	0.577	0.280
Waist/hip ratio	0.97±1.99	1.14±0.53249	1.31±0.491	<0.001*	<0.001*
BMI (kg/m^2)	31.9±1.99	37.47+2.91	40.75+4.61	<0.001*	<0.001*
FMI (kg/m^2)	10.95±1.348	12.76±1.058	14.9+1.33	<0.001*	<0.001*
FFMI (kg/m^2)	20.58+3.64	22.7+2.8	26.95+3.29	<0.001*	<0.001*
Systolic blood pressure (mmHg)	142.1±18.52	139.3±16.89	140.6±15.97	0.438	0.706
Diastolic blood pressure (mmHg)	78.8±7.47	79.5±6.74	81.5±7.696	0.662	0.105
Total cholesterol (mg/dl)	182.7±59.5	213.3±62.22	209.2±53.81	<0.001*	<0.001*
Triglycerides (mg/dl)	169.3±89.18	238.2±85.95	232.2±67.01	<0.001*	<0.001*
LDL cholesterol (mg/dl)	114.3±39.4	149.2±44.26	159.2±29.7	<0.001*	<0.001*
HDL cholesterol (mg/dl)	43.02±11.82	35.76±8.1	33.28±9.57	0.078	0.062
FPG (mg/dl)	89.7±6.56	116.3±6.1	191.5±23.55	0.086	0.681
MoCA	25.2±1.16	25.8±1.56	26.3±1.3	<0.001*	<0.001*
CSF opening pressure (mm H_2O)	250.7±16.56	317.7±29.56	360.7±68.56	<0.001*	<0.001*

CSF, cerebrospinal fluid; FFMI, fat free mass index; FMI, fat mass index; FPG, fasting plasma glucose; Mo CA, Montreal Cognitive Assessment. $Significant *P* value as compared with group I obese patients. #Significant P value as compared with group I obese patients.

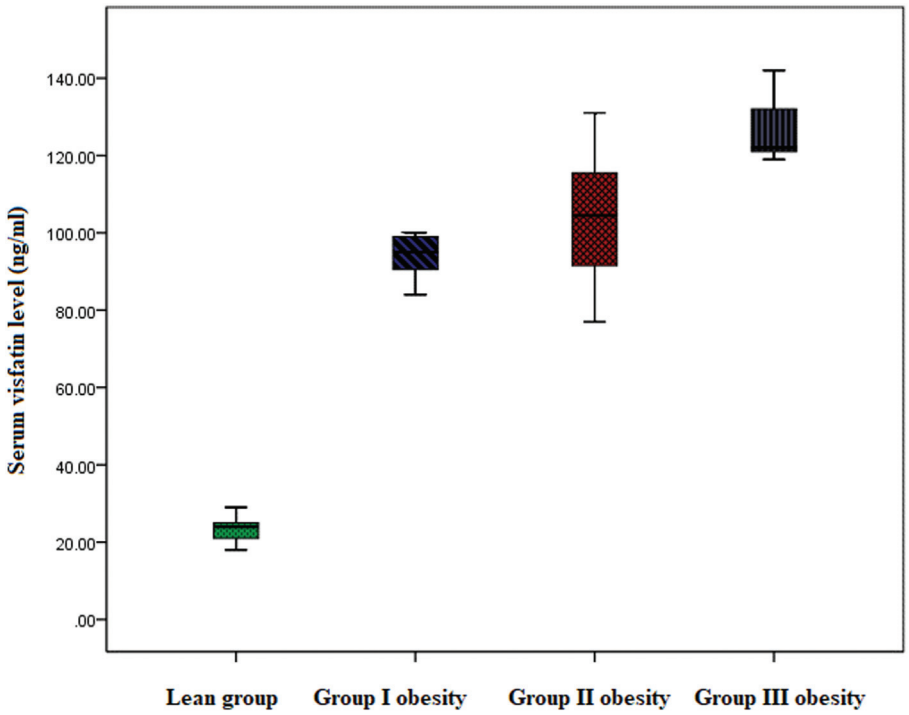
Pearson correlation between visfatin serum (ng/ml) and gene expression levels with clinical and laboratory manifestations in obese women

There was a statistically positive correlation between both serum visfatin and gene expression levels and FMI, FFMI, BMI, FPG, MoCA, and CSF opening pressure (P<0.001*) (Table 3).

Linear regression analysis in the obese group

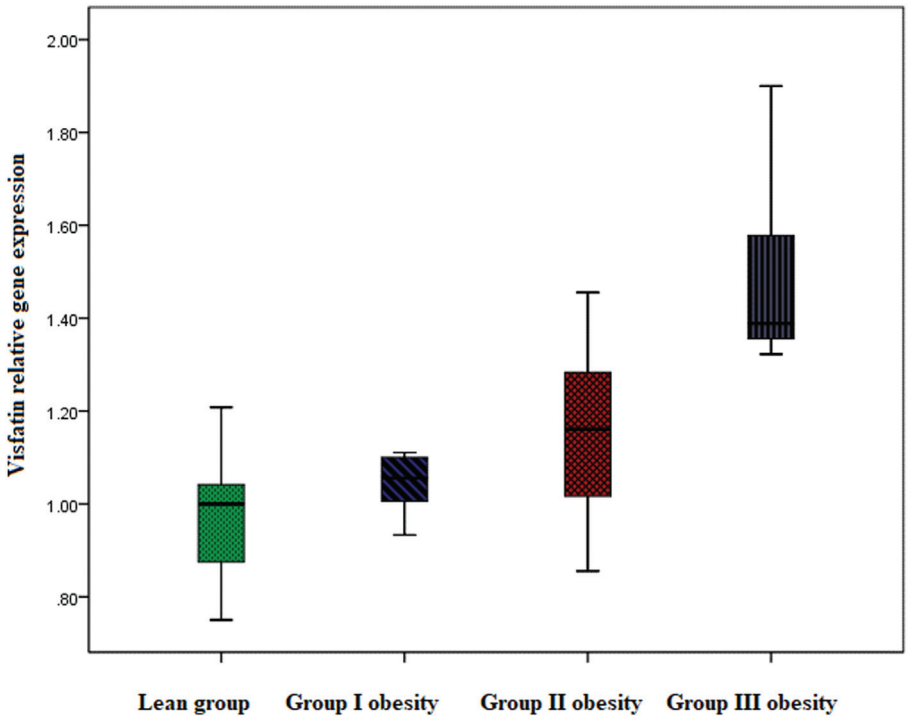
In the obese group, linear regression analysis revealed that BMI, FPG, and CSF opening pressure were independently correlated with serum visfatin and gene expression levels among other clinical and laboratory biomarkers (P<0.001*) (Table 4).

Figure 2



Comparison of visfatin serum (ng/ml) levels in studied groups.

Figure 3



Comparison of visfatin gene expression levels in studied groups.

Table 3 Pearson's correlation coefficient of visfatin circulatory and gene expression levels with other studied parameters among obese patients

	Serum visfatin	Visfatin expression
SBP (mmHg)		
r	0.064	0.465
P	0.408	0.407
DBP (mmHg)		
r	0.107	0.080
P	0.163	0.298
FMI%		
r	0.572	0.577
P	<0.001*	<0.001*
FFMI%		
r	0.568	0.676
P	<0.001*	<0.001*
BMI		
r	0.259	0.220
P	<0.001*	<0.001*
Triglycerides (mg/dl)		
r	0.041	0.008
P	0.599	0.919
HDL-C (mg/dl)		
r	–0.007	–0.041
P	0.932	0.596
FPG (mg/dl)		
r	0.527	0.676
P	<0.001*	<0.001*
MoCA		
r	0.267	0.312
p	<0.001*	<0.001*
CSF opening pressure (mm H_2O)		
r	0.815	0.625
p	<0.001*	<0.001*

CSF, cerebrospinal fluid; FFMI, fat free mass index; FMI, fat mass index; FPG, fasting plasma glucose; Mo CA, Montreal Cognitive Assessment. $Significant *P* value as compared with group I obese patients. #Significant *P* value as compared with group I obese patients.

The accuracy of serum visfatin level (ng/ml) in differentiating obese women from lean ones

We further analyzed our results by the ROC test. The AUC was 0.983 (95% CI =0.962–1.000) with sensitivity of 97.5% and specificity of 75%, at a cutoff value of 99.5 (Fig. 4).

The accuracy of visfatin gene expression level in differentiating obese women from lean ones

We further analysis our results by the ROC test. The AUC was 0.857 (95% CI =0.776–0.939), with sensitivity=87.5% and specificity=85%, at a cutoff value of 1.105 (Fig. 5). Thus, according to our findings, the diagnostic power of serum visfatin in differentiating obese from lean was the highest compared with visfatin gene expression level.

Discussion

Mounting evidence indicates that IIH is a syndrome of raised intracranial pressure, with normal CSF composition and normal brain parenchyma, without any ventriculomegaly or mass lesion. It is associated with obesity and most commonly occurs in women of childbearing age. Previously, this clinical condition was known as benign intracranial hypertension, and the term had gone out of use because of its potential for causing visual loss and poor quality of life [24].

There was great evidence that cognitive function is not frequently emphasized during clinical evaluation of patients with IIH. The exact pattern of cognitive impairment in those patients and its frequency is still controversial [25]. Generally, impaired function in memory, visuospatial skills, learning, concentration, executive functions, and language was found [26,27]. Recently, cognitive affection in IIH could be owing to neurophysiologic disorders [28].

We in this study attempted to pierce out the association between obesity and IIH as well as cognitive dysfunction. Our results revealed that approximately 60% of obese women had IIH and 34% of obese women had cognitive dysfunction, and both IIH and cognitive dysfunction positively correlated with BMI. Regarding the clinical characteristics associated with IIH, the prevalence of headache was the highest among other clinical manifestations.

In accordance with our finding, Almarzouqi *et al.* [29] conducted their study on a Middle East population, and they found a high prevalence of IIH in obese patients.

On the contrary, Asian studies showed a nonsignificant association between obesity and IIH. These studies were mostly done on Korean, Japanese, and Chinese populations where the overall rate of obesity is also low [30–32].

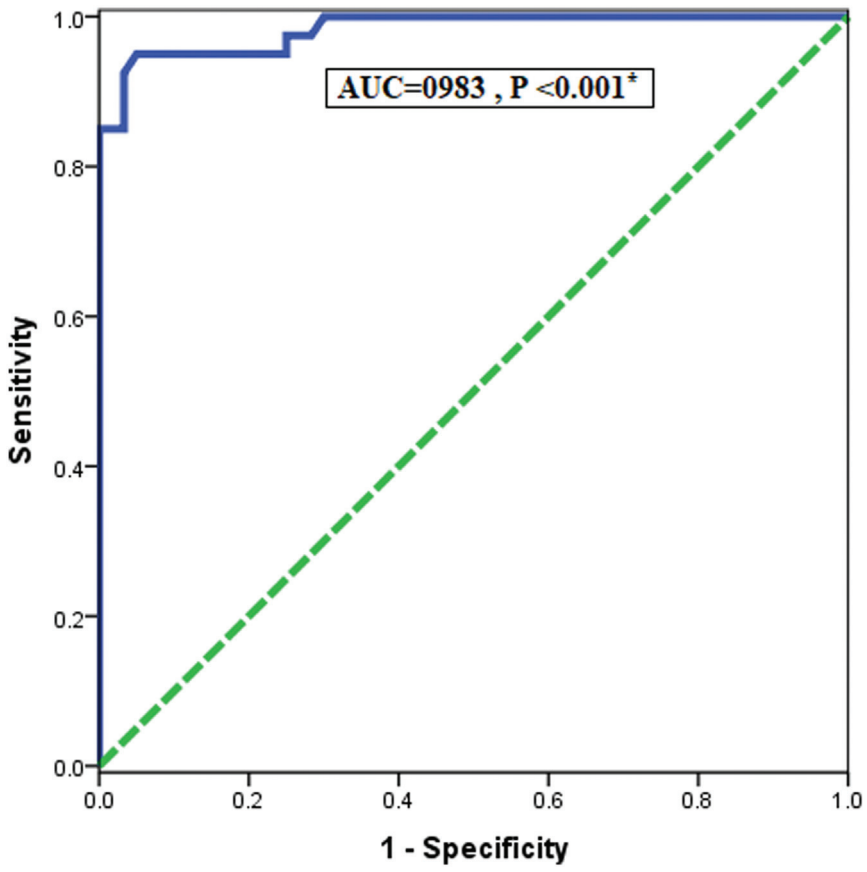
Identifying a successful biomarker depends inevitably on fully understanding the pathophysiology underlying the disease. In obesity and associated complications, despite remarkable advances in the insight into the responsible mechanisms, the etiology remains unknown. This drawback leads to the mandatory search for diagnostic or preclinical biomarkers. The current research therefore increasingly focuses on the discovery of novel biomarker profiles to further elucidate the complex pathophysiology of obesity-related complications. The results presented here are innovative, as this study was the first Egyptian study that investigated the possible association of visfatin gene expression and serum levels with IIH and cognitive dysfunction among obese Egyptian women.

Table 4 Linear regression analyses to test the influence of the main independent variables against visfatin circulatory and gene expression levels (dependent variable) in obese patients.

Model	Unstandardized coefficients	SE	Standardized coefficients	*t*	*P* value	95% CI	
	B		*β*			Lower bound	Upper bound
Serum visfatin							
(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
SBP	0.001	0.001	0.104	1.659	0.099	0.000	0.003
BMI	0.028	0.004	0.551	6.946	<0.001*	0.020	0.036
FPG	0.012	0.002	0.466	4.815	<0.001*	0.007	0.016
CSF opening pressure	0.817	0.190	0.422	4.299	<0.001*	1.192	0.442
TC	0.008	0.006	0.102	1.335	0.184	0.004	0.019
TG	0.008	0.005	0.189	1.593	0.113	0.002	0.018
Visfatin expression							
(Constant)	31.56	13.951		2.263	0.025	59.122	4.017
DBP	0.003	0.008	0.021	−0.355	0.723	0.018	0.013
SBP	0.007	0.004	0.103	1.837	0.068	0.001	0.014
FPG	0.189	0.019	0.702	9.841	<0.001*	0.151	0.227
FMI	0.055	0.011	0.425	4.884	<0.001*	0.033	0.078
CSF opening pressure	4.43	0.895	0.430	4.950	<0.001*	6.200	2.665
TC	0.023	0.027	0.058	0.850	0.397	0.031	0.077
TG	0.038	0.024	0.171	1.597	0.112	0.009	0.085

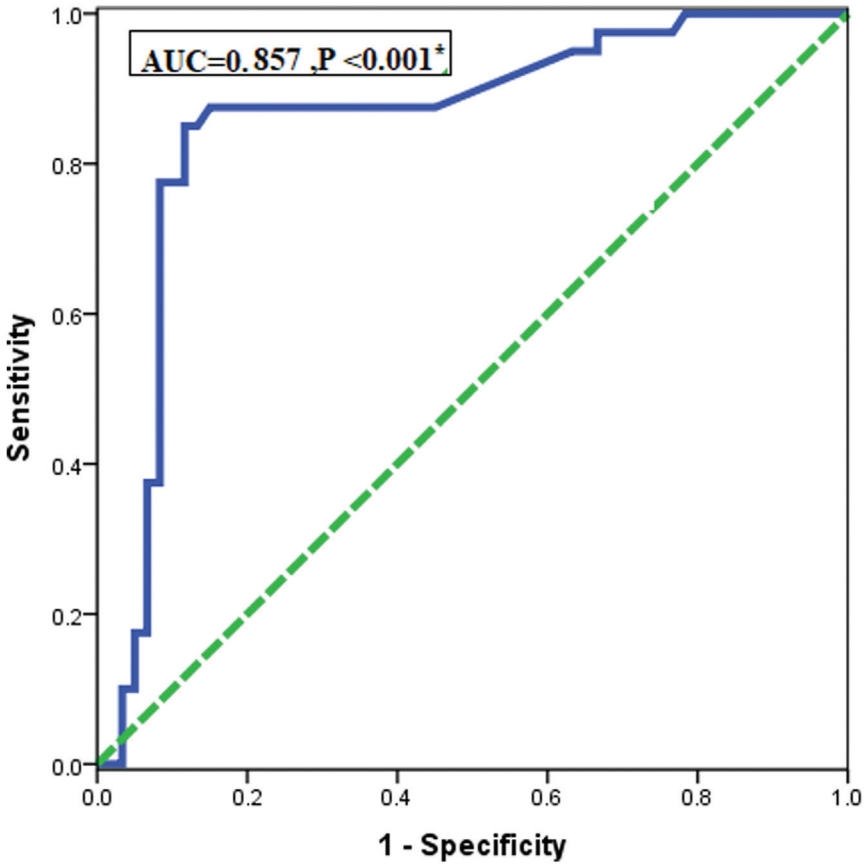
CI, confidence interval; CSF, cerebrospinal fluid; DBP, diastolic blood pressure; FMI, fat mass index; FPG, fasting plasma glucose; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Figure 4



Receiver operating characteristic curve of serum visfatin (ng/ml) levels for differentiating obese women from lean ones.

Figure 5



Receiver operating characteristic curve of visfatin gene expression levels for differentiating obese women from lean ones.

Past decades have witnessed a spurt in research activity that has shown a key role of inflammation in the pathogenesis of obesity and its complication. As expected, our finding adds to the growing body of evidence implicating that obesity is associated with vascular changes, insulin resistance, and inflammation. The most important finding of our study was that MoCA and CSF opening pressure were significantly higher in the obese groups compared with lean controls. We further subgrouped our obese patients according to grades of obesity, and we found that MoCA and CSF opening pressure were significantly higher in morbid obesity compared with mild obesity.

An interesting study conducted by Kerwin *et al.* [33] detected that the cognitive performance of women with a low waist-to-hip ratio decreased as their BMI increased, whereas the cognitive performance of women with a high waist-to-hip ratio increased as the BMI increased.

A study by Elias *et al.* [34] found that nonobese women and obese women scored comparably on various cognitive function tests (e.g. word fluency, visual reproduction, and digit span forward/backward), and the adverse outcome of obesity on cognitive function was limited to men only.

An interesting study from Cekmez *et al.* [35] identified higher levels of plasma visfatin in women with polycystic ovary syndrome. Moreover, another study conducted by Kowalska *et al.* [36] detected higher levels of serum visfatin in lean and obese women with polycystic ovary syndrome.

According to a study on normal-weight females with polycystic ovary syndrome by Zhang *et al.* [37], their results did not find any statistically significant differences between the studied groups regarding the plasma level of visfatin and its gene expression levels in the peripheral blood. The discrepancy between these studies could be explained in part by the effect of the obesity.

In line with this, Curat *et al.* [38] detected that macrophages from visceral white adipose tissue expressed higher levels of visfatin than did mature adipocytes.

In this context, Dahl *et al.* [39] observed increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis.

An interesting Egyptian study conducted by El-Taweel *et al.* [40] observed that pregnant women with hypertension had a lower level of visfatin gene expression compared with normal pregnant women. In earlier published studies, Adya *et al.* [41] suggested that visfatin-induced NF-κB signaling in human endothelial cells affects the activation of gelatinases MMP-2 and MMP-9, suggesting an important role of visfatin in the pathogenesis of vascular inflammation in obesity and type 2 diabetes. There is evidence from previous studies that MCP-1 is pivotal in modulating visfatin-induced angiogenesis via NF-κB and PI3Kinase pathways [42].

The interesting finding of the present study is that there was a positive correlation of serum visfatin and gene expression levels with obesity measures and MoCA. To better understand the association of serum visfatin and gene expression, we further analyzed our results by linear regression analysis, which revealed through linear regression analysis that BMI, FPG, and CSF opening pressure were independently correlated with serum visfatin and gene expression levels among other clinical and laboratory biomarkers. Interestingly, ROC analyses revealed that serum visfatin and gene expression levels could be used as useful biomarkers discriminating obese from lean participants.

In line with this, the study conducted by Li *et al.* [43] observed higher levels of visfatin plasma levels among patients in the headache-attack-period group compared with the healthy control group; these results suggest that visfatin is involved in the process of migraine headache attacks and likely promotes the occurrence of headache attacks.

The probable mechanism between a high-level expression of visfatin and an acute migraine attack may be owing to that high level of visfatin upregulates the transcriptional activity of NK-κB, and then some inflammation factors, such as adhesion molecules (VCAM-1, ICAM) and nitric oxide synthase (iNOS), and thus promotes the occurrence of a headache attack [44].

Conclusion

Visfatin gene expression and serum levels were higher in obese Egyptian women compared with the lean control group. Moreover, there was a strong independent association between higher visfatin expression and serum levels with obesity indices, metabolic risks, IIH, and cognitive dysfunction.

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflicts of interest.

References

1 World Health Organization. Obesity and overweight. Available at: http://www.who.int/mediacentre/ factsheets/fs311/en/www.who.int/topics/obesity/en (Accessed 5 October 2017)

2 Badran M, Laher I. Obesity in Arabic-speaking countries. J Obes 2011; 24:1–9.

3 Fru¨hbeck G. Obesity: screening for the evident in obesity. Nat Rev Endocrinol 2012; 8:570–572.

4 Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384:766–781.

5 Mokdad AH, Ford ES, Barbara A, Bowman Ali, Dietz WH, Frank Vinico F, *et al.* Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003; 289:76–79.

6 Giuseppe V, Wall M, Siegel PZ, Rojas PB. Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. Neurology 1991; 4(Pt 1):239–244.

7 Wall M. Idiopathic intracranial hypertension (pseudotumor cerebri). Curr Neurol Neurosci Rep 2008; 8:87–93.

8 Wall M, George D. Idiopathic intracranial hypertension.A prospective study of 50 patients. Brain 1991; 114(Pt 1A):155–180.

9 Friedman DI. Pseudotumor cerebri. Neurol Clin 2004; 22:99–131.

10 Henouda AS, Metti F, Nouri M. Blindness in idiopathic intracranial hypertension. J D Ophtalmol 2007; 30:588.

11 Hess LM, Insel KC. Chemotherapy-related change in cognitive function: a conceptual model. Oncol Nurs Forum 2007; 34:981–994.

12 Shefer G, Marcus Y, Stern N. Is obesity a brain disease?. Neurosci Biobehav Rev 2013; 37:2489–2503.

13 Yaffe K. Metabolic syndrome and cognitive decline. Curr Alzheimer Res 2007; 4:123–126.

14 Suemoto CK, Gilsanz P, Mayeda ER, Glymour MM. Body mass index and cognitive function: the potential for reverse causation. Int J Obes 2015; 39:1383–1389.

15 Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth Jr, *et al.* Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol 2009; 66:336–342.

16 Moschen AR, Kaser A, Enrich B, Mosheime BA, Theurl M, Niederegger H, *et al.* Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol 2007; 178:1748–1758.

17 Gligor R, Zdremtan D, Pilat L, Tîrgovi CI, Gold VI, Davila C, *et al.* Correlation of visfatin with the lipidic metabolism in diabetic and obese patients. Proc Rom Acad 2012; 1:37–43.

18 Fukuhara A, Matsuda M, Nishizawa M, Katsumori Segawa K, Tanaka M, Kishimoto K, *et al.* Visfatin a protein secreted by visceral fat that mimics the effects of insulin. Science 2005; 307:426–430.

19 Sommer G, Garten A, Petzold S, Beck-Sickinger AG Blüher M, Stumvoll M, *et al.* Visfatin/PBEF/Nampt: structure, regulation and potential function of a novel adipokine. Clin Sci (Lond) 2008; 115:13–23.

20 20.Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology 2002; 59:1492–1495.

21 Rahman TT, El Gaafary MM. Montreal Cognitive Assessment Arabic version: reliability and validity prevalence of mild cognitive impairment among elderly attending geriatric clubs in Cairo. Geriatr Gerontol Int 2009; 9:54–61.

22 Smith T, Gildeh N, Holmes C. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. Can J Psychiatry 2007; 52:329–332.

23 Frieldewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. Clin Chem 1972; 18:499–502.

24 Friedman DI, Rausch EA. Headache diagnoses in patients with treated idiopathic intracranial hypertension. Neurology 2002; 58:1551–1553.

25 Sørensen PS, Thomsen AM, Gjerris F. Persistent disturbances of cognitive functions in patients with pseudotumor cerebri. Acta Neurol Scand 1986; 73:264–268.

26 26.Kaplan CP, Miner ME, Mcgregor JM. Pseudotumour cerebri: risk for cognitive impairment. Brain Inj 1997; 11:293–303.

27 Yri HM, Fagerlund B, Hysse Birgitte F, Jensen RH. Cognitive function in idiopathic intracranial hypertension: a prospective case–control study. BMJ Open 2014; 4:e004376.

28 Elbanhawy IA, Ramzy GM, Basheer MA, Khedr DM. Neurophysiological tests screening cognitive impairment in idiopathic intracranial hypertension patients. Egypt J Neurol Psychiat Neurosurg 2018; 54:7.

29 Almarzouqi SJ, Morgan ML, Lee AG. Idiopathic intracranial hypertension in the Middle East: a growing concern. Saudi J Ophthalmol 2015; 29:26–31.

30 Kim TW, Choung HK, Khwarg SI, Hwang JM, Yang HJ. Obesity may not be a risk factor for idiopathic intracranial hypertension in Asians. Eur J Neurol 2008; 15:876–879.

31 Liu IH, Wang AG, Yen MY. Idiopathic intracranial hypertension: clinical features in Chinese patients. Jpn J Ophthalmol 2011; 55:138–142.

32 Mungreiphy NK, Dhall M, Tyagi R, Saluja K, Kumar A, Tungdim MG, *et al.* Ethnicity, obesity and health pattern among Indian population. J Nat Sci Biol Med 2012; 3:52–59.

33 Kerwin DR, Zhang Y, Kotchen JM, Espeland MA, Linda Van Horn LV, Mctigue KM, *et al.* The cross-sectional relationship between body mass index, waist-hip ratio, and cognitive performance in postmenopausal women enrolled in the Women's Health Initiative. J Am Geriatrics Soc 2010; 58:1427–1432.

34 Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. Int J Obes Relat Metab Disord 2003; 27:260–268.

35 Cekmez F, Cekmez Y, Pirgon O, Canpolat FE, Aydinöz S, Metin Ipcioglu O, Karademir F. Evaluation of new adipocytokines and insulin resistance in adolescents with polycystic ovary syndrome. Eur Cytokine Netw 2011; 22:32–37.

36 Kowalska I, Straczkowski M, Nikolajuk A, Adamska A, Karczewska-Kupczewska M, Otziomek E, *et al.* Serum visfatin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome. Hum Reprod 2007; 22:1824–1829.

37 Zhang J, Zhou L, Tang L, Xu L. Plasma visfatin levels and mRNA expression of visfatin in peripheral blood mononuclear cells and peripheral blood monocyte-derived macrophages from normal-weight females with polycystic ovary syndrome. Exp Ther Med 2014; 7:1215–1220.

38 Curat CA, Wegner V, Sengenes C, Miranville A, Tonus C, Busse R, Bouloumie A. Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. Diabetologia 2006; 49:744–747.

39 39.Dahl TB, Yndestad A, Skjelland M, Øie E, Dahl A, Michelsen A, *et al.* Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis: possible role in inflammation and plaque destabilization. Circulation 2007; 115:972–980.

40 El-Taweel HMA, Salah NA, Selem AK, El-Refaeey AA, Abdel-Aziz AF. visfatin gene expression and oxidative stress in pregnancy-induced hypertension. Egypt J Basic Appl Sci 2018; 5:69–74.

41 Adya R, Tanb K, Chen J, Randeva HS. Nuclear factor-kappa B induction by visfatin in human vascular endothelial cells: Its role in MMP-2/9 production and activation. Diabetes Care 2008; 31:758–760.

42 Adya R, Tanb K, Chen J, Randeva HS. Pre-B cell colony enhancing factor (PBEF)/visfatin induces secretion of MCP-1 in human endothelial cells: role in visfatin-induced angiogenesis. Atherosclerosis 2009; 205:113–119.

43 Li C, Zhu Q, He Q, Wang J, Wang F, Zhang H. Plasma levels of cyclooxygenase-2 (COX-2) and visfatin during different stages and different subtypes of migraine headaches. Med Sci Monit 2017; 23:24–28.

44 Sarchielli P, Floridi A, Mancini ML, Rossi C, Coppola F, Baldi A, *et al.* NF-kappaB activity and iNOS expression in monocytes from internal jugular blood of migraine without aura patients during attacks. Cephalalgia 2006; 26:1071–1079.