Influence of Disordered Eating on Serum Nesfatin, Female Reproduction, and Metabolic Feature in Patients With Diabetes

Original Article

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ABSTRACT

Background: Eating disorders (EDs) can cause significant disturbance of the menstrual cycle and impaired female fertility. The comorbidity of EDs in T1DM leads to poorer glycemic control and subsequently more complications. Nesfatin-1 performs an important role in controlling food intake, gastrointestinal motility, glucose homeostasis, and reproductive functions. We aimed in the current research to explore the serum nesfatin-1 levels in female patients with diabetes, and also to assess the influence of disordered eating on its levels, metabolic, and reproduction features.

Materials and Methods: We conducted a case-control study on 70 participants (30 patients with DM and 40 control group). We selected 20 female patients with T1DM and 10 patients with T2DM. Both groups suffer from EDs and reproductive dysfunctions. Serum nesfatin-1 levels were measured.

Results: Women with DM had significantly lower values of Serum nesfatin-1 (ng/mL) (0.70±0.2) compared to controls (2.21±0.391), $P < 0.001$. Interestingly, there was a non-significant difference between female patients with T1DM (0.83±0.33) from other group T2DM (0.63±0.08) regards serum nesfatin-1, $p = 0,332$. Duration of diabetes, HbA1c, estradiol, and LH scores were independently associated with serum nesfatin-1. Remarkably, we detected that the sensitivity and specificity of serum nesfatin-1 values for distinguishing EDs from the other group among female patients with DM were 96.3% and 99%, respectively.

Conclusion: Nesfatin-1 levels were found to be significantly lower in female patients with DM compared to the control group and negatively correlated with cardiometabolic risk factors as well as EDs pattern and reproductive dysfunction parameters.

Key Words: Diabetes, disordered eating, dysfunction, infertility, nesfatin, reproductive.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease that seriously endangers human health, with a rapidly growing prevalence worldwide an estimated 90–95% of DM cases are type 2 diabetes[1]. It is worth noting that both type 1 and type 2 diabetes are associated with reproductive disorders for example delayed puberty, menstrual cycle irregularities, infertility, metabolic problems during pregnancy, and premature ovarian insufficiency[2].

There is growing evidence that eating disorders (EDs) cause significant morbidity and elevated mortality in women at childbearing age[3,4] As a matter of fact, women with EDs are often able to conceive despite serious menstrual irregularities and after recovery, gonadal functioning normalizes in most case[5]. Though, it is assumed that lifetime EDs are associated with infertility[6].

Despite advances in the diagnosis and management of DM, it is not particularly surprising to detect a high prevalence of fertility disorders among patients with DM in particular female patients. Among T1DM female patients interesting research detected that the concomitant occurrence of autoimmune thyroid diseases and T1DM could be one of the most important risk factors of fertility disorders among T1DM patients as these patients suffering from hypothyroidism and premature ovarian failure[7].

Nowadays, it is widely recognized that subfertility and infertility in the female with T2DM are not related to the age of patients and menstrual irregularity, but it could be owed to obesity and metabolic dysfunction which leads to ovulatory dysfunction and poor-quality blastocysts[8].

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In addition to appetite and weight regulation, several pieces of evidence have shown that serum nesfatin-which is widely expressed all over the body for example pancreatic tissue, pituitary gland, adipose tissue, and stomach and has an important role in reproduction and metabolic regulation[9]. Thus, we aimed in the current research to explore the serum nesfatin-1 levels in female patients with diabetes, and also to assess its correlation with the pattern of EDs as well as the metabolic and reproduction features.

PATIENTS AND METHODS

After receiving approval from the Ethical Committee of the Faculty of Medicine, Zagazig University with (IRB no.10481). All contributors gave informed consent before they participated in the study. We enrolled 30 female patients with DM and 40 healthy age-adjusted females as the control group. We designated the current study as a case-control study, and we conducted the current study on 30 patients with DM mainly university students who attempt outpatient clinic of Zagazig University hospitals. As expected T1DM patients were more prevalent than T2DM thus, 20 female patients with T1DM and 10 patients with T2M were enrolled in the study. Both groups suffering from EDs and reproductive dysfunctions. The flowchart of the study is described in (Figure 1). The diagnosis of eating disorders was established according to Structured Clinical Interview for DSM-IV-TR axis I disorders (SCID I)[10], the Arabic version[11], and the Arabic version of the Eating Disorder Examination Questionnaire (EDE-Q)[12,13].

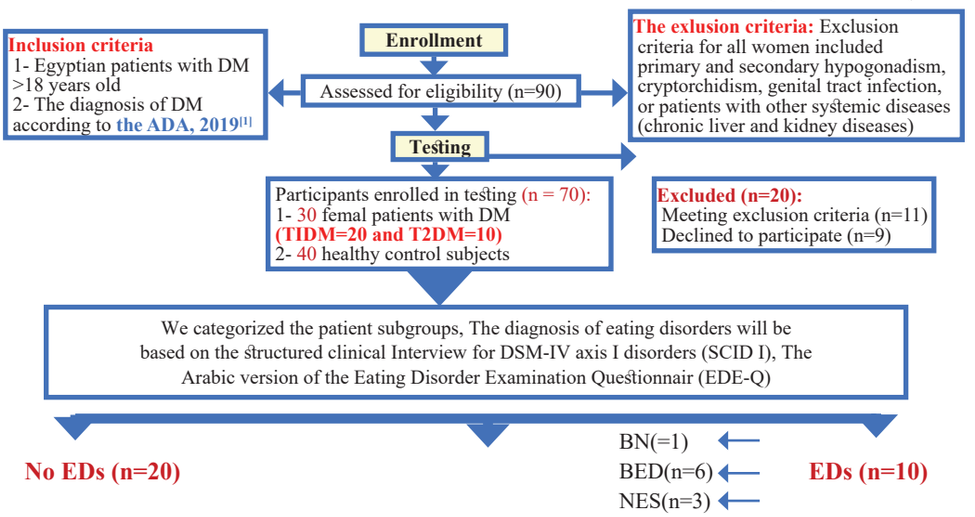

Fig. 1: Flowchart of the study

Biochemical tests

Blood samples were taken from all members during the early follicular phase of the menstrual cycle and testing was done according to operating techniques in Zagazig university hospital laboratories. The concentration of nesfatin-1 in serum was determined using an EIA kit (the kit was supplied via EIAab Science Co. Ltd. E-PP-1585).

Statistical analysis:

All analyses were conducted using SPSS version 26, and $P < 0.05$ was considered statistically significant. For descriptive characterization, we used t-tests and Mann-Whitney-U-tests. For descriptive characterization, frequencies were calculated using crosstabs followed by $\chi 2$-tests. Correlations between serum nesfatin-1and studied parameters were done.

RESULTS

3.1. Clinical, demographic, and EDs characteristics of all studied women

The design of the current study was a case-control study, and we conducted the current study on 30 patients with DM mainly university students who attempt outpatient clinic at Zagazig University hospitals. As expected, a large fraction of the women in our study suffered from T1DM (n=20). There were statistically significant differences between studied groups regards systolic blood pressure, diastolic blood pressure, BMI, family history of diabetes mellites, duration of diabetes, gravidity, and parity. Interestingly, we presented the frequencies of reproductive disorders complaints among female patients with DM in (Figure 2). For further evaluation of the current study results, we presented the prevalence of abnormal EDE-Q scores among female patients with Diabetes Mellites in (Figure 3).

Concerning EDs prevalence among studied groups, the total number of female patients with DM and had EDs according to DSM-IV-TR criteria, was 10 patients; one woman had bulimia nervosa (BN), six women had binge eating disorder (BED) and three women had night eating syndrome (NES). (Table 1, $P < 0.05$).

3. 2. laboratory characteristics of the studied groups

There was a significant difference between female patients with DM compared to control regards, fasting

plasma glucose, HbA1c, ovarian volume, AFC, LH, LH/FSH ratio, AMH, anti-TPO, and anti-TG, $P < 0.001$. However, estradiol, and SHBG values were significantly high in the control group compared to the group with DM, (Table 2, $P < 0.05$).

3.3. Comparison of serum nesfatin-1 in studied groups

The current study detected that women with DM had significantly lower values of Serum nesfatin-1 (ng/mL) (0.70 ± 0.2) compared to controls (2.21±0.391) (Table 1, $P < 0.001$). Interestingly, there was a non-significant difference between female patients with T1DM (0.83±0.33) from other group T2DM (0.63±0.08)regards serum nesfatin-1 (ng/mL), $p = 0,332$, (Figure 4).

3.4. Correlation between serum nesfatin-1 clinical, metabolic features, reproductive parameters and eating patterns among patients with DM.

Interestingly we observed in the current research that among the DM group, there were significant negative correlations between serum nesfatin-1 and duration of diabetes, body mass index, fasting plasma glucose, HbA1c, LH, AMH, and total testosterone. On the other hand, there were significant positive correlations between serum nesfatin-1 and estradiol and SHBG (Table3, $P < 0.05$).

3.5. Linear regression analysis

To further validate the present study results, we used linear regression, and we detected that duration of diabetes, HbA1c, estradiol, and LH scores were independently associated with serum nesfatin-1 (Table 4, $P < 0.05$).

3.6. The accuracy of serum nesfatin-1 values for distinguishing EDs from the other group among female patients with DM

Remarkably we detected that the AUC of nesfatin-1 was 0.960 (95% CI = 0.907-1.000) with sensitivity = 96.3%, specificity = 99%, and cutoff values (1.24), $P < 0.05$), (Figure 5).

Table 1: clinical, demographic and EDs characteristics of all studied women.

Characteristics	Control group (n=40)	Patients with DM (n=30)	*P*
Age (years)	29.2±5.96	28.7±5.9	*0.849*
Systolic blood pressure (mm Hg)	118.1±8.7	138.3±17.6	*< 0.001**
Diastolic blood pressure (mm Hg)	75.7±4.14	95.64±14.21	*< 0.001**
Body mass index (kg/m2)	28.6±5.9	37.9±4.6	*< 0.001**
Family history of diabetes mellites	4(10%)	10 (33.3%)	*< 0.001**
Type of DM			*< 0.001**
T1DM	0(0%)	20(66.7%)	
T2DM	0(0%)	10(33.3%)	
Duration of diabetes(y)	0(0%)	13±4.5	*< 0.001**
Gravidity			
Nulligravid	4(10%)	12(40%)	*< 0.001**
1	10(25%)	13 (43.3%)	
2+	28(70%)	8(26.7%)	
Parity			
Nulliparous	4(10%)	12(40%)	*< 0.001**
1	10(25%)	13 (43.3%)	
2+	28(70%)	5(16.7%)	
Prevalence of abnormal EDE-Q score			
Global Scale	1(2.5%)	6(20%)	*<0.001**
Restraint Subscale	1(2.5%)	4(13.3%)	*<0.001**
Shape Concern Subscale	5 (12.5%)	19(63.3%)	*<0.001**
Weight Concern Subscale	4 (10%)	11(36.6%)	*<0.001**
Eating Concern Subscale	1(2.5%)	3(10%)	*<0.001**
HADS score			
Anxiety	6.81±3.56	8.63±3.66	*<0.001**
Depression	3.64±3.21	5.19±2.98	*<0.001**
DSM-IV-TR diagnoses			
All ED diagnoses	6 (15%)	10(33.3%)	*<0.001**
BN	1(2.5%)	1(3.3%)	*<0.001**
BED	3(7.5%)	6(20%)	*<0.001**
NES	2(5%)	3(10%)	*<0.001**

Complications		
Retinopathy	0(0%)	5(16.7%)
Neuropathy	0(0%)	6(20%)
Nephropathy	0(0%)	3(10%)
Stroke	0(0%)	1(3.3%)
CHD	0(0%)	0(0%)
Medications		
Oral	0(0%)	7(23.3%)
Insulin	0(0%)	23(76.7%)

DSM-5; the diagnostic and statistical manual of mental disorders, Fifth Edition, BN; bulimia nervosa, BED; binge eating disorder, NES; night eating syndrome *$P < 0.05$ when compared with control group.

Table 2: laboratory characteristics of the studied groups

Characteristics	Control group (n=40)	Patients with DM (n=30)	*P*
Fasting plasma glucose (mg/dL)	110.3±45.85	136.5±58.15	*< 0.001**
HbA1c	5.07±0.208	9.13±3.1	*< 0.001*
TSH (µIU/ml)	2.94±1.76	2.74±1.5	*0.848*
Prolactin (ng/mL)	12.38±0.721	12.49±1.44	*0.521*
Ovarian volume	5.62±1.5	8.2±4.675	*< 0.001**
AFC	5.79±2.766	8.1±2.39	*< 0.001**
FSH (mIU/mL)	4.80±0.55	4.98±0.49	*0.556*
LH (mIU/mL)	6.00±1.93	12.32±3.77	*< 0.001**
LH/FSH ratio	1.08±0.13	2.52±0.52	*< 0.001**
AMH (ng/mL)	2.32 ±0.64	4.32±1.64	*< 0.001**
DHEA-S (µg/dl)	192.0 ± 33.02	234.0 ± 63.02	*< 0.001**
Total testosterone (ng/ml)	0.57±0.24	0.56±0.32	*0.132*
Free testosterone (pg/ml)	0.74±0.14	0.95±0.22	*0.167*
Estradiol (pg/ml)	44.86 ± 24.34	29.86 ± 12.34	*< 0.001**
SHBG (nmol/l)	26.40±6.10	13.40±3.10	*< 0.001**
Anti TPO(IU/ml)	1.78±0.74	157.5 ± 43.3	*< 0.001**
Anti TG (IU/ml)	3.44 ±0.56	244.0 ± 66.1	*< 0.001**
Serum nesfatin-1(ng/mL)	2.21±0.391	0.70±0.2	*< 0.001**

HbA1c, hemoglobin A1c; TSH, thyroid stimulating hormone; AFC, antral follicle count; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, Anti-Müllerian Hormone; DHEA-S, dehydroepiandrosterone sulfate; SHBG; sex hormone binding globulin

Table 3: Pearson correlations of serum nesfatin-1 (ng/mL) with characteristics of female women with DM

Parameters	T1DM		T2DM	
	r	*p*	r	*p*
Duration of diabetes	-0.584	*< 0.001**	-0.601	*< 0.001**
Body mass index	-0.551	*< 0.001**	-0.798	*< 0.001**
Fasting plasma glucose	-0.436	*< 0.001**	-0.573	*< 0.001**
HbA1c	-0.649	*< 0.001**	-0.247	*< 0.05**
TSH	-0.042	*0.730*	-0.097	*0.42601**
Prolactin	-0.580	*< 0.001**	-0.747	*< 0.001**
Ovarian volume	-0.396	*0.155*	-0.583	*< 0.001**
AFC	-0.564	*< 0.001**	-0.521	*< 0.001**
LH	-0.554	*< 0.001**	-0.438	*< 0.001**
AMH	-0.827	*< 0.001**	-0.584	*< 0.001**

Free testosterone	-0.128	*0.357*	-0.122	*0.317*
Total testosterone	-0.144	*< 0.001**	-0.097	*0.426*
Estradiol	0.576	*< 0.001**	0.632	*< 0.001**
SHBG	0.754	*< 0.001**	0.463	*< 0.001**
HADS score				
Anxiety	-0.501	*< 0.001**	-0.733	*< 0.001**
Depression	-0.5501	*< 0.001**	-0.446	*< 0.001**

HbA1c, hemoglobin A1c, TSH, thyroid stimulating hormone; AFC, antral follicle count *$P < 0.05$

Table 4: Linear regression analyses to test the influences of the main independent variables against serum nesfatin-1 (ng/mL) (dependent variable).

Model	Unstandardized Coefficients		Standardized Coefficients	t	*p*	95% C.I.	
	B	SE	Beta			Lower Bound	Upper Bound
Constant	0.398	0.059		6.744	*< 0.001**	0.281	0.516
Duration of diabetes	-0.002	0.001	-0.096	-3.287	*< 0.001**	-0.003	-0.001
BMI	-0.007	0.012	-0.031	-0.553	*0.582*	-0.032	0.018
AMH	-0.153	0.075	-0.305	-2.032	*0.046*	-0.304	-0.003
HbA1c	-0.519	0.022	-0.922	23.212	*< 0.001**	-0.563	-0.475
Estradiol	0.280	0.013	1.026	21.014	*< 0.001**	0.254	0.306
AFC	0.003	0.004	0.026	0.854	*0.395*	-0.005	0.011
LH	-0.101	0.040	-0.445	-2.556	*< 0.05**	-0.180	-0.022

BMI, body mass index; HbA1c, hemoglobin A1c; LH, luteinizing hormone; AFC, antral follicle count *$P < 0.05$

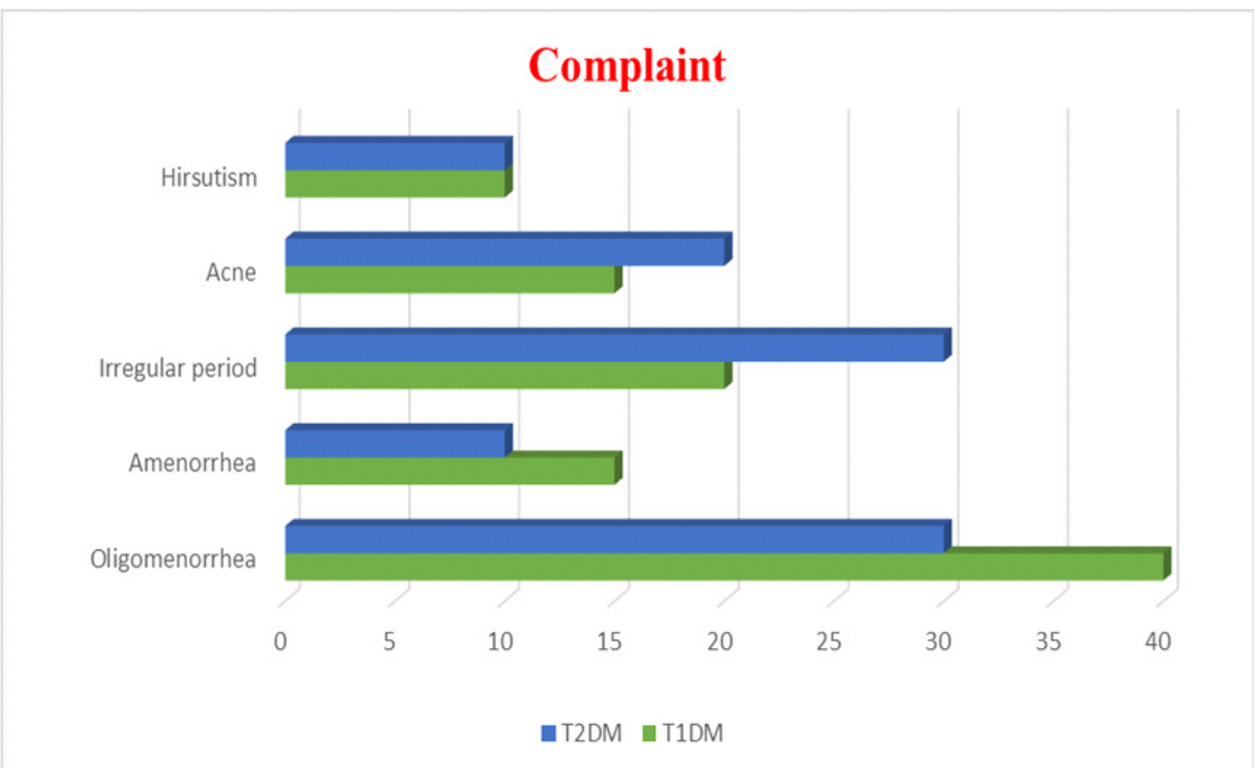

Fig. 2: Frequencies of reproductive disorders complaints among female patients with Diabetes Mellites

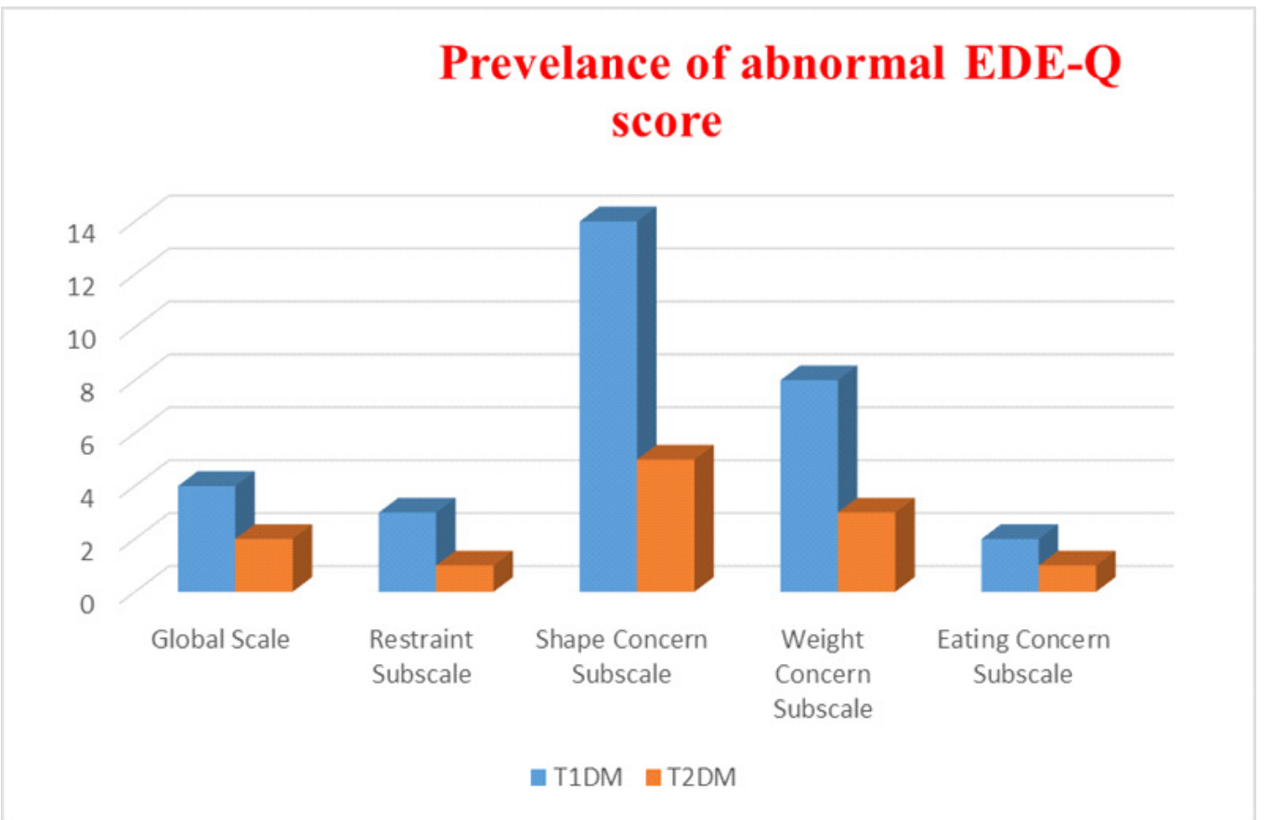

Fig. 3: Prevalence of abnormal EDE-Q score among female patients with Diabetes Mellites

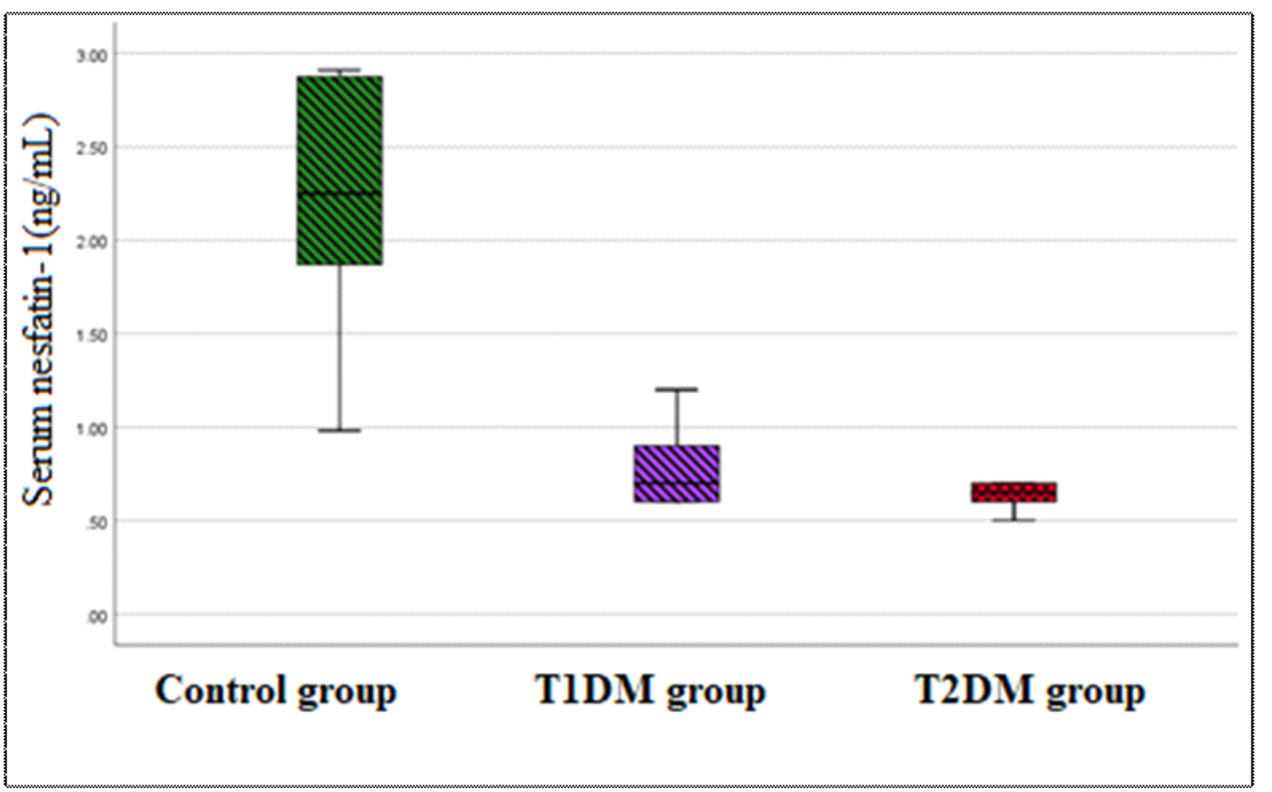

Fig. 4: Comparison of Serum nesfatin-1(ng/mL) among studied groups.

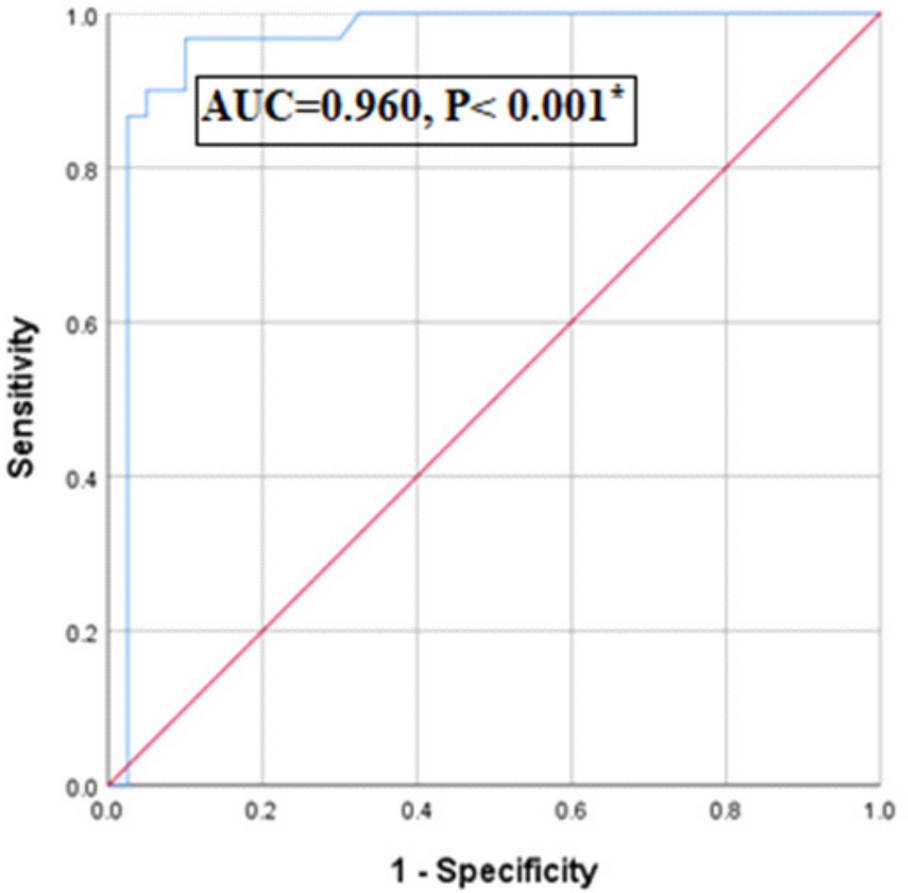

Fig. 5: The accuracy of serum nesfatin-1for characteristic EDs from the other group among female patients with DM

DISCUSSION

Evolving evidence suggests that the diagnosis of ED in patients with T1DM is challenging because eating manners are frequently secreted and denied. In this context, Markowitz *et al* have proposed that the most harmful EDs pattern in patients with T1DM is insulin omission in addition to dietary patterns recommended to patients with DM, for example, low carbohydrate diets, and eating when not hungry[14].

There is evidence that nesfatin-1 plays an essential role in regulating food intake, gastrointestinal motility, glucose homeostasis, arterial blood pressure, stress, and reproductive functions[15]. Intriguingly, it has been reported that serum nesfatin-1 is expressed in female reproductive organs[16]. Consequently, we intended in the current research to investigate the serum nesfatin-1 levels in female patients with diabetes, and also to assess its correlation with the metabolic and reproduction features of patients with both DM and EDs.

As we have mentioned before we conducted the current study on 30 patients with DM mainly university students who attempt outpatient clinic of Zagazig University hospitals thus, our enrolled female patients with diabetes mainly suffer from T1DM. As expected, metabolic and reproductive dysfunction markers were significantly high compared to healthy control. Regards the frequencies of reproductive disorders complaints among female patients with DM, we detected that the most prevalent complaints were oligomenorrhea and irregular menses in both T1DM and T2DM.

These results were consistent with Shim *et al*, who detected that menstrual irregularity was associated with female patients with T2DM[17]. Similar results were observed in the Kelsey *et al* study, they discovered that adolescent females with T2DM had menstrual irregularity[18].

Interestingly, the current research detected that the shape and weight concern subscale was the most prevalent EDE-Q score among female patients with DM. Concerning EDs prevalence among studied groups, the total number of female patients with DM who had EDs according to DSM-IV-TR criteria was 10 patients. Remarkably, BED was the most prevalent EDs among female patients with DM.

In our research, we focused on markers of fertility to assess the influence of both DM and EDs on reproduction and we detected that there was a significant difference between female patients with DM compared to control regards, fasting plasma glucose, HbA1c, ovarian volume, AFC, LH, LH/FSH ratio and AMH. moreover, we detected significantly positive thyroiditis autoantibodies; anti-TPO and anti-TG. A study performed by Strotmeyer *et al*. observed that more than 40% of women with Type 1 diabetes had autoimmune thyroiditis[19].

Similar results were observed by interesting research they found that women with EDs had a significantly high prevalence of reproductive disorders compared to the general population[20-24].

The most important findings of the current study were that females with DM had significantly lower values of serum nesfatin-1 compared to controls. Interestingly, there was a non-significant difference between female patients with T1DM from other groups with T2DM regards serum nesfatin-1.

Studies have also verified that Nesfatin-1 is a part of the HPG axis and involved in gonadal functions and reproduction. Furthermore, experimentally studied detected that nesfatin-1 was expressed in the ovary[25].

In line with the current results, Li *et al* found that nesfatin-1values were significantly lower in T2 DM patients compared to healthy subjects and T1 DM patients[26]. Similar results were detected in a recently published Egyptian study conducted on drug-naive patients with DMT2 and pre-diabetes in addition to the control group, and they found that serum nesfatin-1 was significantly lower in the diabetic and pre-diabetic compared to the control group. Also, diabetic patients had statistically significantly lower nesfatin-1 levels than pre-diabetic patients[27].

Additionally, our results found that there were significant negative correlations between serum nesfatin-1 and duration of diabetes, body mass index, fasting plasma glucose, HbA1c, BMI, LH, AMH, and total testosterone, as well as the scores of anxiety and depression. on the other hand, there were significant positive correlations between serum nesfatin-1 and estradiol and SHBG. Therefore, it is interesting to investigate the most independently associated with serum nesfatin-and we detected that duration of diabetes, HbA1c, estradiol, and LH scores were independently associated with serum nesfatin-1. The accuracy of serum nesfatin-1 values for characteristic EDs from the other group among female patients with DM, surprisingly, we detected that the sensitivity and specificity were 96.3% and 99%, respectively.

Matta *et al* study confirmed that nesfatin-1 was negatively correlated with cardiometabolic risk factors in both diabetic and pre-diabetic. Additionally they detected that the sensitivity of nesfatin-1 was 96.7 and 100%, and specificity of 93.3% and 96.7% for the diagnosis of pre-diabetes and diabetes respectively.

CONCOLUSION

In conclusion, the current study is the first study to investigate the association between EDS patterns and metabolic as well as reproductive dysfunctions in patients with DM in correlation with serum nesfatin-1 levels. We found that serum nesfatin-1 was significantly lower in female patients with DM compared to control. nesfatin-1 was significantly negatively correlated with metabolic, reproductive, and EDs parameters.

CONFLICT OF INTEREST

There are no conflicts of interests.

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