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Serum leptin level in diabetic patients with erectile dysfunction

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ABSTRACT

Background: Erectile dysfunction (ED) is a common sexual problem affecting men. Diabetes mellitus (DM) is one of the most common comorbidities of ED. Leptin is a 167-amino-acid peptide that is mainly expressed in white adipose tissue but is also found in a variety of tissues. **Objective:** To estimate serum level of leptin in diabetic patients with ED and correlate level of serum leptin in diabetic patients with severity and origin of ED. **Patients and methods:** Cross-sectional descriptive study was conducted on 64 individual male; 34 diabetic patients of both types of DM with ED and 30 non diabetic normal erectile function as control. All patients were evaluated clinically by history included IIEF-5 score and examination. Assessment of serum leptin level, HbA1c, cholesterol, triglycerides was done and penile duplex study was done only for diseased patients. **Results:** Serum leptin significantly increased in cases than control (P <0.001). Also, there was increased in diabetic men vasculogenic ED either arterial, venous or mixed (P =0.047). Serum leptin was correlated with the severity of ED (P =0.046). **Conclusion:** Leptin may play an important biomarker as a cost-effective method for diagnosis and assessment of severity of vasculogenic ED in DM and as a good predictor for ED occurrence.

Keywords: Diabetes mellitus, Erectile dysfunction, Serum leptin.

INTRODUCTION

Erectile dysfunction (ED) is the failure to attain or maintain a satisfactory penile erection for sexual intercourse [(1)]. It is a common problem affecting 15% of men in the age range of 40 to 50 years, 45% of men in their 60s, and 70% of men older than 70 years [(2)]. ED is classified into organic and psychogenic subtypes, of which the organic subdivision is often caused by a variety of factors including diabetes mellitus (DM), hypertension, cardiovascular diseases, and hyperlipidemia [(3)].

ED is known to be one of the pressing problems faced by people with diabetes. About 75% of men who live with diabetes are exposed to ED in their earlier ages as compared to non-diabetic men [(4)]. DM was able to produce oxidative stress damage in cavernosal tissues, usually resulting in the loss of the physiological properties of endothelium and shifting to a vasoconstrictor, pro-thrombotic and pro-inflammatory state [(5)].

Leptin was discovered as the product of obese (*ob*) gene, which is located on the long arm of 7th chromosome [(6)]. The peripheral actions of leptin include stimulation of inflammatory reaction, oxidative stress, atherogenesis and thrombosis, thus promoting endothelial dysfunction, arterial stiffness, development and vulnerability of atherosclerotic plaques [(7, 8)].

Aim of this study was to estimate serum level of leptin in diabetic patients with ED and correlate level of serum leptin in diabetic patients with severity and origin of ED.

PATIENTS AND METHODS

This is a cross-sectional descriptive study, which was performed between August 2018 and May 2019 at the Department of Dermatology, Venereology and Andrology at Aswan University Hospital.

Ethical approval: An informed consent was taken from all patients. **The study was approved from Ethics Committee, Faculty of Medicine, Aswan University.**

Patients with other causes of ED including pelvic trauma, pelvic surgical intervention, hypogonadism, hyperprolactinemia, smoking and old age more than 60 years were excluded from our study.

The study involved 64 individual male enrolled by Diabetic Outpatient Clinic and Andrology Outpatient Clinic complaining of ED. It included 34 diabetic patients. The patients were of both type of DM and their age ranged from 28-60 years. It also included 30 non diabetic normal erectile function as control, their age ranged from 21-45 years. Each patient was assessed by complete history, general, and genital examination. In IIEF-5 score (International Index of Erectile Function-5 items) [(9)] each item is scored from 0 to 5 on four items and 1 to 5 in one item. Disease grades of ED on IIEF-5 scores were categorized as follows: severe ED (IIEF-5 score: 1-7), moderate ED (IIEF-5 score: 8-11), mild to moderate ED (IIEF-5 score: 12-16), mild ED (IIEF-5 score: 17-21), and no ED (IIEF-5 score: 22-25). Investigations done for both diseased and control were as follows: serum leptin measured by enzyme immunoassay method, triglycerides, cholesterol level,

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while penile duplex study was performed only for diseased group where participants were classified into groups as follow: group 1 diabetic with arteriogenic ED, group 2 diabetic with venogenic ED, group 3 diabetic arteriogenic and venogenic ED, group 4 diabetic with psychogenic ED.

Sample size calculation:

Sample size calculation was carried out using G*Power 3 software [(10)]. A calculated minimum sample of 60 patients was needed. The sample was divided into two groups (30 Diabetic with ED (A) and 30 Control group (C), which was needed to detect an effect size of 0.2 in the mean serum level of leptin, with an error probability of 0.05 and 90% power on a two-tailed test.

Statistical analysis

Data were verified, coded by the researcher and analyzed using SPSS version 21. Descriptive statistics: Means, standard deviations, medians, range, and percentages were calculated. Test of significances: For continuous variables; independent t-test analysis was carried out to compare the means of normally distributed data, while one-sample t-test was calculated to test the difference between mean and single measurement.

The clinical and demographic factors with proven statistical significance from the univariate analyses were further included in the multivariate logistic regression models. For variables with more than two categories; ANOVA test was calculated. Post-hoc test was calculated using Bonferroni corrections. Correlation analysis was used to test the association between variables (Pearson's correlation). A p-value equals or less than 0.05 was considered significant.

RESULTS

Sociodemographic and laboratory data are shown in table 1. Regarding HbA1c, cholesterol, IIEF-5 score and serum leptin, there was statistically significant difference between cases and control and no change in age and triglycerides.

Table 1: Sociodemographic and Laboratory Data Differences between Cases and Controls

Parameter (Mean ± SD)	Control (No.=30)	Case (No.=34)	P-value
Age/years	33.22 ± 6.7	36.03 ± 6.3	= 0.089
HbA1c	5.23 ± 0.5	8.38 ± 1.9	**< 0.001**
Triglycerides	99.37 ± 18.4	113.60 ± 21.7	< 0.007
Cholesterol	135.83 ± 43.7	167.55 ± 41.1	**= 0.004**
S. Leptin	3.64 ± 0.2	21.58 ± 3.9	**< 0.001**
IIEF-5 score	25	8.53 ± 4.2	**< 0.001****

Multiple logistic regression analyses for ED are shown in table 2.

Table 2: Independent Erectile Dysfunction Predictors: Logistic Regression Model

Variable	Univariate		Multivariate	
	OR (95% CI)	P-value	HR (95% CI)	P-value
• **Age/years**	1.033 (0.983–1.086)	= 0.201		
• **HbA1c**	12.058 (2.717–53.510)	**= 0.001**	3.298 (1.481–9.506)	**= 0.012**
• **TGD**	1.009 (0.995–1.023)	= 0.206		
• **Cholesterol**	1.018 (1.005–1.031)	**= 0.007**	1.017 (0.961–3.024)	= 0.181
• **Serum Leptin**	1.662 (1.201–2.299)	**= 0.002**	7.554 (2.212–13.038)	**< 0.001**

OR, Odds Ratio; CI, Confidence Interval

Classification of patients according to pharmaco-penile duplex ultrasonography (PPUD) study is shown in table 3.

Table 3: Classification of cases according to Colour Coded Duplex

Variable	Category	n = 34
Erectile Dysfunction Cause	**Normal**	4 (11.8%)
	Arteriovenogenic	5 (14.7%)
	Arteriogenic	10 (29.4%)
	Venogenic	15 (44.1%)
Total		**34 (100%)**

The results of IIEF-5 scale of the studied cases is shown in table 4.

Table 4: IIEF-5 scale of the studied cases

Variable	Category	n = 34
IIEF-5 score	• **Mean ± SD**	8.53 ± 4.2
	• **Median (Range)**	9 (2 - 16)
IIEF-5 Categories	• **Mild ED (17-21)**	0 (0%)
	• **Mild to Moderate ED (12-16)**	9 (26.5%)
	• **Moderate ED (8-11)**	10 (29.4%)
	• **Severe ED (1-7)**	15 (44.1%)

(IIEF-5= international index of erectile function -5, SD=standard division, n= number**)**

There was statistically significant correlation between serum leptin and disease duration and IEF-5 score among cases (Table 5).

Table 5: Correlation between HbA1C, Disease Duration, IIEF Score and Serum Leptin among Cases

	HbA1c		Dis. Duration		S. Leptin	
	r*	**P-value**	**r**	**P-value**	**r**	**P-value**
HbA1c	1					
Disease Duration	**0.507**	**= 0.001**	**1**			
S. Leptin	0.017	= 0.233	**-0.204**	**= 0.047**	**1**	
IIEF-5 Score	-0.176	= 0.160	**-0.242**	**= 0.046**	**-0.219**	**= 0.05**

*Pearson's correlation coefficient

The mean of serum leptin in the diseased groups according to PPUD was statistically significant, while between each 2 diseased groups there was a statistical significant difference between normal (psychogenic ED) and arteriogenic ED, normal and venogenic ED, and normal and mixed type of ED (Table 6).

Table 6: Serum Leptin Level Difference in Diseased Groups according to Duplex Findings

	Normal (I) (n=4)	Mixed (III) (n=5)	Arterial (II) (n=10)	Venous (IV) (n=15)	P-value
Serum Leptin (ng/ml)					
• **Mean ± SD**	**14.53 ± 2.7**	**20.80 ± 4.2**	**22.89 ± 5.9**	**22.84 ± 4.6**	**0.047***
• **Median (Range)**	**6 (3 - 46)**	**10 (6 - 50)**	**16 (1.5 -57)**	**19 (3 - 60)**	
P-value	**I vs. II =0.039**	II vs. III =0.625	I vs. IV =0.996	**I vs. IV =0.032**	
	I vs. III =0.031	II vs. IV =0.461			

Correlation of serum leptin and the severity of ED according to IIEF-5 was statistically significant in groups according to the mean of serum leptin, and there was a statistical significant difference in serum leptin between mild-moderate and moderate group, and between mild-moderate and severe group (Table 7).

Table 7: Serum Leptin Level Difference in Diseased Groups according to IIEF-5 Categories

	Mild-Mod. (I) (n=16)	Moderate (II) (n=7)	Severe (III) (n=5)	P-value*
Serum Leptin (ng/ml)				
Mean ± SD	**11.46 ± 2.6**	**29.23 ± 4.6**	**22.55 ± 4.7**	**= 0.046***
Median (Range)	**7.5 (1.5 - 36)**	**30 (5 -60)**	**22 (3– 57)**	
P-value**	**I vs. II =0.034**	II vs. III =0.364	**I vs. III =0.043**	

DISCUSSION

Diabetic men have a well-known increased risk of developing ED, with prevalence rates ranging from 35% to 90% [11]. Diabetic men display a three times probability of having ED than men without diabetes; moreover, the age-adjusted risk of ED was doubled in diabetic men than in those without diabetes. ED occurs 10–15 years earlier in men with diabetes [12].

The most common cause of ED is vasculogenic type and it may be a marker for occult cardiovascular disease. Vasculogenic ED does not rule out the presence of contributing psychological factors, but merely means that vascular factors are the predominant cause. PPDU evaluation of cavernosal arteries after intracavernosal injection of vasodilating agent is particularly useful in the evaluation of vasculogenic causes [13].

Leptin is considered one of the adipokines, which involved in various metabolic processes, such as energy metabolism, inflammatory response, and vascular function. Dysregulation of adipokines production results in the generation of ROS and induces endothelial dysfunction [14]. Leptin has been associated with atherosclerotic and thrombotic disease [15].

In our study, serum leptin level was higher in cases than control group, which agreed with, **Wang *et al.*** [16] who found that mean leptin level in patients was higher than that in the healthy controls after adjusting for BMI. Putting in consideration body fat mass assessed by BMI, **El-Haggara *et al.*** [17] investigated the correlation between serum leptin in obese and non-obese diabetic patients with ED where it was higher in obese patient than non-obese.

According to ED predictors, logistic regression model was conducted to predict the occurrence of ED using age, HbA1c, triglycerides, cholesterol and serum leptin. They were all significant except for age and triglycerides in univariate model and only HbA1 and serum leptin were significant in multivariate model.

In our study, the mean age of the patients was insignificant predictor for ED. Although, the effect of age on ED is not surprising as rising age is associated with ED, as was shown in several studies [18, 19]. No significant relation was detected in our study and this was in agreement with [20], who found that increasing age has an invariant effect.

Poor glycemic control as demonstrated by HbA1c in this study was found to be significant predictor for ED. This trend was demonstrated severally by other studies, which showed a relationship between poor glycemic control and ED [21, 22]. Whereas other studies did not report any association [23]. **El-Sakka and Tayeb** [24] reported that diabetic patients with poor metabolic control were over 12 times more likely to report ED than diabetics with good control. This association may be due to a positive link between blood glucose levels and endothelial dysfunction [25].

Epidemiologic data confirmed that hyperlipidemia is a strong independent risk factor for the development of ED via endothelial damage and inflammation [26].

In our study we found that cholesterol and triglycerides were different. Cholesterol only was significant predictor for ED as was found before by [27, 28].

While triglycerides is showing controversial results in association with ED. No correlation was found in our study as in [29], but this disagreed with **Corona *et al.*** [30] who found that high TG levels are associated with arteriogenic ED and concluded that triglycerides is independent predictor for ED.

Serum leptin according to our study was highly significant predictor for ED. Although a few studies were done regarding correlation of the leptin with ED, **Wang *et al.*** [16] concluded the potential value of leptin in diagnoses of ED.

Plasma leptin level correlated with increased metabolic syndrome components [31]. Plasma leptin level in diabetes is rather controversial; one study does not observe any significant difference between diabetic and non-diabetic subjects [32].

In our study, serum leptin level had significant correlation with DM duration and it was higher in diabetic patients than control but no correlation was found between serum leptin level and glycemic control in diabetic patients.

On the light of these observations in the relation of leptin action and pathogenesis of the ED where endothelial dysfunction occurs as end result, and independently of body fat mass, we can claim that no other studies earlier to ours studied the correlation of leptin in a diabetic patient with ED and normal, but most studies instead discussed the relation of obesity with ED or leptin level in ED patients and its grades.

On studying the correlation of serum leptin level difference in groups according to color penile duplex, we found a significant increase in serum leptin in diabetic men with vasculogenic ED; either arterial, venous or mixed, which agreed with, **Dozio *et al.*** [33] who observed that serum leptin is higher in arteriogenic ED patients than non arteriogenic ED, as they divided the cases according to presence or lack of ED into these two categories.

In comparing serum leptin between different grades of ED patients according to IIEF-5; in our study we found significant correlation of mean serum leptin among the groups and between each 2 groups; being lower in mild-moderate group in comparison with moderate and severe groups. These findings were in agreement with **Wang *et al.*** [16], who found that leptin level is high in these groups but was lower in mild than others.

This was in disagreement with **El-Haggara *et al.*** [17], who found that serum leptin between different grades of ED patients according to IIEF-5 showed no significant differences.

CONCLUSION

In conclusion, we investigated the serum leptin level in diabetic patients with ED and its relation with vascular ED. Leptin represented one of the causes of vascular endothelial dysfunction, which is concedered as main cause in DM vascular complication and ED, so leptin might be associated with vasculogenic ED in diabetic patients. Leptin may play an important biomarker as a cost-effective method for diagnosis and assessment of severity of vasculogenic ED in DM and as a good predictor for ED occurrence.

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