

## Serum Homocysteine Level as A Marker of Erectile Dysfunction

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### ABSTRACT

**Background:** The Fourth International Consultation on Sexual Medicine defined erectile dysfunction (ED) as a consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction homocysteine (Hcy) is a toxic, nonproteogenic sulfur-containing amino acid synthesized from dietary methionine in the liver and is metabolized either via trans-sulfuration or remethylation pathway.

**Objective:** To investigate serum Hcy levels in ED patients as compared to those in healthy controls, and to explore its correlation with severity of ED.

**Patients and methods:** This study consisted of 30 ED-affected men and 50 age-matched controls who were free from ED. All participants were recruited from the Andrology Outpatient Clinic of Mansoura University Hospital, between October 2019 and September 2020.

**Results:** Serum Hcy was significantly higher in ED cases compared to controls ( $P < 0.001$ ). The mean of serum Hcy in cases was  $24.17 \pm 11.502 \mu\text{mol/L}$  versus  $8.43 \pm 9.076 \mu\text{mol/L}$  in controls. 23 out of 30 ED cases (76.66 %) had hyperhomocysteinemia ( $> 15 \mu\text{mol/L}$ ). On the other hand, 6 out of 50 controls (12 %) had elevated level of Hcy. Elevation of Hcy levels was associated with an increased risk of ED, and that a cut-off value of  $8.28 \mu\text{mol/L}$  was able to detect ED patients with a corresponding sensitivity and specificity of 90.0% and 78% respectively.

**Conclusion:** Elevated Hcy is associated with ED and may represent an important risk factor and play a pathophysiologic role in ED. Hence, Hcy-lowering agents, such as folic acid and vitamin B12, seem reasonable choices for the prevention and management of this condition.

**Keywords:** Homocysteine, Erectile dysfunction.

### INTRODUCTION

Erectile dysfunction (ED) is a major health problem that becomes increasingly prevalent with age, and seriously affects the quality of life and self-esteem of patients and their partners <sup>(1)</sup>. A wide range of disorders are associated with increased concentrations of Hcy.

The proposed mechanisms of the association include angiotoxicity, neurotoxicity, and inhibition of collagen cross-linking <sup>(2)</sup>. Elevated serum Hcy has been linked to impaired endothelial function and occlusive vascular disease <sup>(3)</sup>. ED and cardiovascular disease share the same principal risk factors considered to induce vascular endothelial damage <sup>(4)</sup>. Hyperhomocysteinemia could also be involved in the pathogenesis of ED, and there is a growing body of evidence supporting the close correlation between hyperhomocysteinemia and ED <sup>(5)</sup>. Increased Hcy could inhibit NOS, probably influencing the production of NO, and the development of ED <sup>(4)</sup>. Meanwhile, hyperhomocysteinemia was shown to be a risk factor for ED and endothelial dysfunction in rat models <sup>(6)</sup>. It was assumed that Hcy might be a risk factor for ED in men <sup>(6,7,8)</sup>. However, the role of Hcy in the development of ED is still putative, and it is not clear whether Hcy actually plays a causal role in ED with which it is associated, or rather a marker of some other underlying mechanism. Data suggests that Hcy is a marker for the presence of pathological oxidant stress <sup>(7)</sup>. Thus, it is possible that hyperhomocysteinemia is not

a common primary cause of ED, but rather a marker of endothelial oxidant stress that is a major mediator of this disorder. Hcy can cause cellular injury via oxidative damage <sup>(9)</sup>, which is a major mechanism responsible for vascular dysfunction in hyperhomocysteinemic animals' model that is made by genetic or dietary means <sup>(10)</sup>, and in humans with massive elevation of Hcy as seen in homocysteinuria<sup>(11)</sup>.

Severe forms of hyperhomocysteinemia are commonly due to major genetic mutations of the enzymes implicated in the Hcy metabolism (e.g., MTHFR polymorphisms), whereas slightly elevated Hcy values are more frequently caused by vitamin deficiencies and environmental factors <sup>(12)</sup>. Several studies suggest Hcy may be an independent risk factor for ED <sup>(6,7)</sup>. The aim of the present study was to investigate serum Hcy levels in ED patients as compared to those in healthy controls, and to explore its correlation with severity of ED.

### SUBJECTS AND METHODS

This prospective case-control study was conducted in the Outpatient Clinic of Dermatology, Andrology, and STDs Department (Andrology Unit), Mansoura University Hospital, between October 2019 and September 2020.

Cases group included 30 men with ED who consecutively attend the Andrology Outpatient Clinic. A control group of 50 age-matched healthy men with



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normal erectile function were recruited from volunteer healthy hospital staff at Dermatology Outpatient Clinic of Mansoura University Hospital. Cases and controls were recruited from the same geographic area (Dakhliya, Egypt).

#### Ethical consent:

Written informed consent had been obtained from all the patients and healthy controls after the objectives and methods of the study were explained to them. Study protocol was approved by the Institutional Review Board (IRB) of Mansoura Faculty of Medicine. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

**Inclusion criteria:** (1) Heterosexual men with ED: patients reporting difficulty in attaining or maintaining erection for at least 6 months, and having a score of less than 22 in the International Index of Erectile Function (IIEF-5) questionnaire. (2) Age between 20 and 50 years. (3) All participants were sexually active, in a stable and heterosexual partnership, living with their sexual partner for at least the past one year, and had only one sexual partner. (4) The frequency of trying sexual intercourse was  $\geq 1$ /week. (5) Healthy weight: body mass index between 18.5 – 24.9 kg/m<sup>2</sup>. (6) Normal constant healthy eating habits.

**Exclusion criteria:** (1) Refusal to participate. (2) A primary diagnosis of another sexual disorder, and serious relationship problems. (3) Smoking, drugs, alcohol, or substance abuse. (4) Use of nutritional supplement like multivitamins (within 120 days), which might influence Hcy levels. (5) Risk factors known to disturb methionine metabolism (diabetes mellitus, hypertension, cardiac disease, respiratory disease, renal disease, chronic liver disease, neurological disease, inflammatory/immune diseases, thyroid disorders, and malignancy). (6) Penile anatomical abnormalities, Peyronie's disease, and previous genitourinary surgery. (7) Major physical illness, psychological or psychiatric disorders. (8) Patients using erection inducing medication, any medication known to cause ED, or drugs that affect vitamin metabolism within 3 months of the start of the study.

#### All patients were subjected to:

- 1) **Detailed personal**, dietary, medical, psychological and sexual history
- 2) **The validated Arabic version Shamloul *et al.*** <sup>(13)</sup> of International Index of Erectile Function (IIEF)-5 **Rosen *et al.*** <sup>(14)</sup> to diagnose the presence and assess the severity of ED. Items in the IIEF-5 are phrased to reference the prior six-month period, which conforms with the NIH's current reference period for establishing a diagnosis of ED. The severity of ED was described as mild, moderate or severe according to the five-item IIEF-5 questionnaire,

with a score of 1–7 indicating severe, 8–11 moderate, 12–16 mild–moderate, 17–21 mild and 22–25 no ED.

- 3) **Calculation of body mass index (BMI):** The weight and height of men were recorded and the BMI was calculated (BMI= weight in Kg/ height in meters<sup>2</sup>).
- 4) **Physical examination: All patients had a full physical examination including:** Secondary sex characters and the presence of gynecomastia. Signs of vitamin deficiency (B<sub>12</sub>, B<sub>6</sub> and folic acid), pallor and peripheral neuropathy. Cardiovascular system: measurement of heart rate, blood pressure and peripheral pulses. Neurological examination to assess possible underlying neurological conditions. Vitamine B complex deficiency. Signs of homocysteinuria.
- 5) **Genital examination:** Penis: size, scars, hypospadias, plaque, or others. Scrotum: color, rugae, or others. Testes: site, volume, sensation, and consistency. Epididymis. Spermatic cords. Digital rectal examination for prostate evaluation and assessment of sphincter tone.
- 6) **Penile color Doppler ultrasonography (PCDU):** After pharmacological stimulation (10 micrograms of the PGE1), and by using a high-resolution color Doppler ultrasound (Mindray DC-N2, Shenzhen Mindray Biomedical Electronics Co, Ltd. Shenzhen, China) equipped with a 5–10 MHz linear probe (75L38EA). Penile evaluation was done first to exclude corporeal fibrosis and Peyronie's plaques and to measure the diameter of both cavernous arteries at the proximal penile shaft.
- 7) **Laboratory Investigations:**
  - Biochemical blood tests: lipid profile, fasting and postprandial blood sugar. Additional tests were performed to verify the inclusion criteria, and exclude any systemic disease as directed by history and clinical examination.
  - Hormonal analysis: total serum testosterone, serum prolactin.
  - Measurement of total serum homocysteine by ELISA kit (Nova human homocystiene ELISA kit, Bioneovan Co., Ltd. Beijing, China). according to the manufacturer's instructions.

#### Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 22.0 (Armonk, NY: IBM Corp.).

Qualitative non-numerical data were described using number and percent. Quantitative data were described using median (minimum and maximum) and inter quartile range for non-parametric data and mean  $\pm$  standard deviation (SD) for parametric data after testing the normality of data distribution using Kolmogorov-Smirnov test. Chi-square test was used for categorical variables, to compare between different groups. Mann-Whitney U test was used for non-parametric

quantitative variables, to compare between two study groups. Receiver-operating characteristics (ROC) curve was used to determine the optimal cut-off point for Hcy (according to the highest sensitivity and specificity).

ROC curve provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups (for Hcy to predict ED cases vs control). Logistic regression analysis and generalized linear model were used for prediction of risk factors. A p-value of  $\leq 0.05$  was considered as statistically significant.

**RESULTS**

The mean age of patients group was  $41.20 \pm 7.84$  years old and that of the control group was  $43.38 \pm$

$7.13$  years old. There was no significant difference between both groups as regards age, duration of marriage, occupation, BMI, blood glucose level, lipid profile and serum prolactin.

A significant difference was found between both groups as regards total testosterone level ( $p = 0.003$ ). Erectile dysfunction was diagnosed according to the five-item IIEF-5 if its score was below 22. There was a highly significant difference ( $p < 0.001$ ) in the mean IIEF-5 score between patients and healthy controls ( $13.10 \pm 3.497$  and  $23.38 \pm 1.176$  respectively) as shown in table (1).

**Table (1):** Demographic characteristics, glucose tolerance, lipid profile, hormonal assay and IIEF-5 score in the studied groups

Variable	ED group (n= 30)	Control group (n= 50)	95 % CI	P
Age (years)	$41.20 \pm 7.845$	$43.38 \pm 7.131$	-5.6 - 1.2	0.206 <sup>1</sup>
BMI (kg/m <sup>2</sup> )	$23.13 \pm 0.744$	$22.85 \pm 1.004$	-0.14 - 0.70	0.190 <sup>1</sup>
Duration of marriage (years)	$8.97 \pm 7.894$	$6.58 \pm 3.807$	-0.23 - 5.0	0.129 <sup>1</sup>
Occupation	Worker	66.7% (20)	-0.28 - 0.15	0.551 <sup>2</sup>
	Employee	33.3 % (10)		
Fasting glucose (mg/dL)	$82.03 \pm 6.441$	$81.90 \pm 8.021$	-3.3 - 3.6	0.939 <sup>1</sup>
Postprandial glucose (mg/dL)	$143.63 \pm 10.094$	$145.42 \pm 14.794$	-7.9 - 4.3	0.561 <sup>1</sup>
Cholesterol (mg/dl)	$175.37 \pm 11.012$	$171.82 \pm 14.829$	-2.7 - 9.8	0.260 <sup>1</sup>
Triglycerides (mg/dl)	$171.40 \pm 14.041$	$164.20 \pm 13.026$	1.0 - 13.4	0.023 <sup>1</sup>
Total testosterone (ng/ml)	$5.69 \pm 1.628$	$4.81 \pm 0.956$	0.3 - 1.5	0.003 <sup>1</sup>
Prolactin (ng/ml)	$8.21 \pm 2.776$	$7.96 \pm 1.846$	-0.8 - 1.3	0.630 <sup>1</sup>
IIEF-5	$13.10 \pm 3.497$	$23.38 \pm 1.176$	-11.4 - -9.2	< 0.001 <sup>1</sup>

Data are expressed as mean and standard deviation. ED=erectile Dysfunction; BMI=Body Mass Index; 95% CI: 95% confidence interval of the mean difference between both groups, IIEF-5, 5-item of the International Index of Erectile Function.

P is significant when  $< 0.05$ . <sup>1</sup> Mann Whitney U test, <sup>2</sup> Chi square test.

Based on PCDU Results, patients were classified into 2 subgroups: patients with normal pharmaco-penile duplex ultrasonography, and thus having a non-vascular ED; and impaired penile vascular function (vasculogenic ED) (Table 2).

**Table (2):** Results of pharmaco-penile duplex ultrasonography

Study group (n= 30)	Mean $\pm$ SD	Median	IQR
PSV (cm/s)	$32.21 \pm 12.836$	30.16	20.74 - 39.33
EDV (cm/s)	$7.17 \pm 3.665$	7.02	4.97 - 10.72
RI	$0.77 \pm 0.085$	0.78	0.72 - 0.81

PSV, peak systolic velocity; EDV, end diastolic velocity; RI, resistant index

**Subtype and severity of ED in the patients group:**

According to IIEF-5 score, ED cases were divided into 6 mild cases (20.0%), 15 mild to moderate cases (50.0 %), 7 moderate cases (23.3%), and 2 severe cases (6.7%). As regards ED subtype; there were 24 cases with vasculogenic ED (80.0%) [14 cases with arteriogenic ED (46.6 %), 10 cases with venogenic ED (33.3%)], and 6 cases with non-vasculogenic ED (20.0%) as shown in table (3).

**Table (3):** Erectile dysfunction (ED) severity and cause in the patients group

ED grade	N	%
Mild	6	20.0 %

(According to IIEF-5 score)	Mild to Moderate	15	50.0 %
	Moderate	7	23.3 %
	Severe	2	6.7 %
ED type	Vasculogenic	24	80.0 %
	Non-vasculogenic	6	20.0 %
Cause of vasculogenic ED	Arteriogenic	14	46.6 %
	Venogenic	10	33.3 %

**Homocysteine (Hcy) levels in the studied groups:**

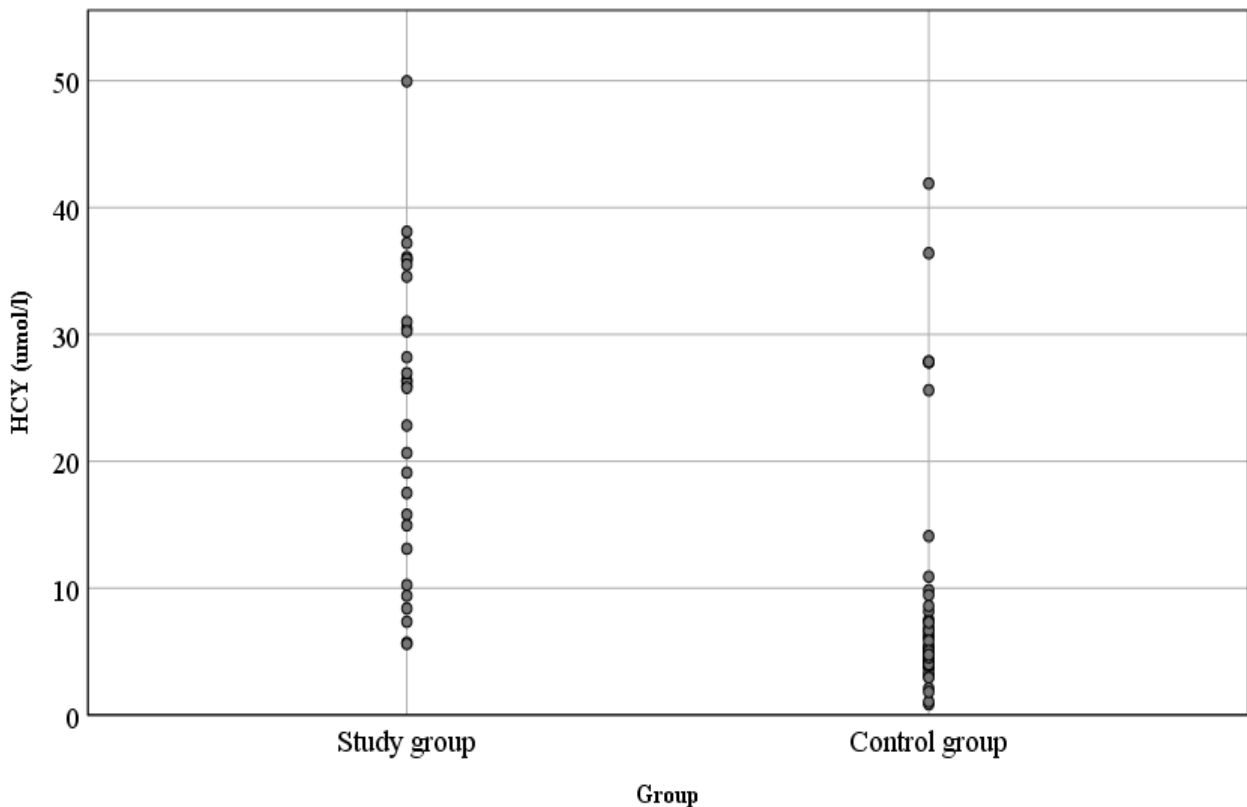
The mean value of serum Hcy was significantly higher in ED cases (24.17  $\mu\text{mol/l}$ ) than those of control group (8.43  $\mu\text{mol/l}$ ), and the difference was statistically highly significant ( $p < 0.001$ ). 23 out of 30 ED cases (76.66 %) had hyperhomocysteinemia ( $> 15 \mu\text{moles/L}$ ). On the other hand, 6 out of 50 controls (12 %) had elevated level of Hcy as shown in table (4) and figure (1).

**Table (4):** Homocysteine levels in the studied groups

	Study group (n = 30)	Control group (n = 50)	95% CI	p
Hcy ( $\mu\text{mol/l}$ )	24.17 $\pm$ 1.502	8.43 $\pm$ 1.076	11.1 - 20.4	<b>&lt; 0.001</b>

Man Whitney U test was used for comparison of numerical parameters; difference between both groups.  $p$  is significant when  $< 0.05$ .

CI: confidence interval of the mean



**Figure (1):** Homocysteine (Hcy) levels in the studied groups

**Post-hoc Power Analysis:** post-hoc power analysis was performed at the completion of the study for *Man Whitney U test* to compute power, alpha was set to .05, total sample size was 80 (30 ED cases + 50 controls),

and effect size (mean Hcy level in ED group was 24.17 and SD was 11.502; while control group mean was 8.43 and SD was 9.076) to tell that sample size was sufficient. Computed required power was 99.9%.

**Table (5):** Univariate logistic regression predicting severity of ED

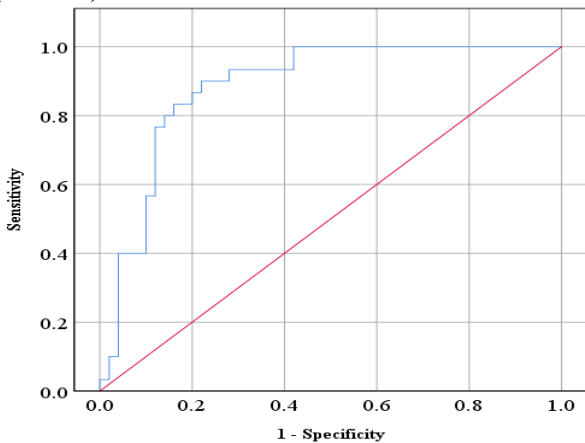
	<b>b</b>	<b>R<sup>2</sup></b>	<b>p</b>
<b>BMI</b>	1.043	0.055	<b>0.036</b>
<b>Triglycerides</b>	-0.109	<b>0.075</b>	<b>0.014</b>
<b>Hcy</b>	-0.329	<b>0.563</b>	<b>&lt; 0.001</b>
<b>RI</b>	33.636	<b>0.269</b>	<b>0.003</b>

The categorical dependent variables were the various ED groups, based on the IIEF-5.  
 b: regression coefficient; R<sup>2</sup>: coefficient of determination (the proportion of variation in Y is being explained by the variation of X); p is significant when ≤ 0.05  
 BMI, body mass index; ED, erectile dysfunction; RI, resistance index; Hcy, homocysteine; IIEF-5, 5-item of the International Index of Erectile Function;

Logistic regression analysis revealed that BMI (*p* = 0.036), triglycerides (*p* = 0.014), Hcy (*p* < 0.001) and RI (*p* < 0.003) were significant predictor risk factors for ED. Higher serum Hcy level was shown as independent predictor of ED severity.

**Diagnostic profile of serum Hcy levels for diagnosis of ED:**

Receiver operating characteristic (ROC) curve of serum Hcy (Fig. 2) was conducted to evaluate the sensitivity and specificity of serum Hcy as a diagnostic index for ED. Serum Hcy showed high accuracy AUC (AUC= 0.885). There was a statistically significant diagnostic value compared to the AUC/ROC value of 0.5 (*p* < 0.001). At best cut off value of 8.28 μmol/L, Hcy was able to predict ED with 90% sensitivity, 78% specificity, positive predicative value (PPV) of 71.1 %, negative predicative value (NPV) of 92.9 %, and accuracy of 82.5 % (Table 6).



**Figure (2):** Receiver operating characteristics (ROC) of Hcy levels for discrimination between erectile dysfunction cases and controls.

**Table (6):** AUC and performance characteristics of homocysteine levels for discrimination between erectile dysfunction cases and control subjects

	<b>ED</b>
<b>Area under the curve (AUC)</b>	0.885
<b>95 % CI of AUC</b>	0.811 - 0.958
<b>p</b>	<b>&lt; 0.001</b>
<b>cut off value ( μmol/l)</b>	8.28
<b>Sensitivity</b>	90.0 %
<b>Specificity</b>	78.0 %

<b>Positive predictive value (PPV)</b>	71.1 %
<b>Negative predictive value (NPV)</b>	92.9 %
<b>Accuracy</b>	82.5 %

**DISCUSSION**

The mean duration of ED in the patients group was 34.0 ± 22.850 months. There was no statistically significant difference between the two study groups regarding blood glucose level, lipid profile and serum prolactin. A significant difference was found between both groups as regards total testosterone level (*p* = 0.003), which is supported by the finding of **Blute et al.** (15) that testosterone deficiency is associated with a decline in erectile function and testosterone levels are inversely correlated with increasing severity of ED.

As regard ED subtype in the current study, there were 24 cases with vasculogenic ED (80.0%) [14 cases with arteriogenic ED (46.6 %) and 10 cases with venogenic ED (33.3%)], and 6 cases with non-vasculogenic ED (20.0%). **Salonia et al.** (16) reported that the most frequent form of ED is vasculogenic, which is consistent with the finding in this study that 80% of ED cases were vasculogenic.

Hyperhomocysteinemia is defined as a plasma Hcy level >15 μmol/L (17). In the present study, the proportion of hyperhomocysteinemia was higher in the ED group (76.66 %) than that in the control group (12 %), and serum Hcy levels were significantly higher (*p* < 0.001) in ED cases (24.17 ± 11.502 μmol/L) when compared to control subjects without ED (8.43 ± 9.076 μmol/L). This result agrees with several investigators reporting significantly higher Hcy levels in ED patients than in controls (8, 18, 19). Although it was not found in **Morley et al.** (20) study. The ambiguous result can, at least partly, be the effect of the small study sizes (resulted in limited statistical power); and the use of different diagnostic criteria of ED and control group in different studies (possibly provide confounding bias). For example, **Morley et al.** (20) adopted penile Doppler ultrasound parameters to define ED and control subjects, as compared to IIEF-5 used in other studies. The sample size was only six in control group of **Morley et al.** (20) study, which resulted in limited statistical power. On the other hand, for the enrollment criteria of control subjects, some studies included subjects with diabetes (5, 21, 22), which is a known risk factor for ED and possibly provide confounding bias. By contrast, in the present study, a precise and strict inclusion and exclusion criteria were established for the enrolment of ED and control subjects. Subjects with any possible factors that may interfere with erectile function, such as diabetes, hypertension and any known history of cardiovascular diseases were excluded in this study in an attempt to increase the validity of the results. A post-hoc power analysis was performed at the completion of the study to tell if sufficient subjects were recruited for the main objective of this study with respect to level of Hcy between the ED group compared to control group (for correctly rejecting the null hypothesis).

There was a highly significant positive correlation between Hcy levels and age of ED cases ( $p < 0.001$ ) in the present study, which is consistent with the population-based Hordaland homocysteine study by **Nygaard et al.** (23) in which Hcy level was shown to increase with age.

In this study, a weak positive statistically non-significant correlation was found between serum Hcy level and postprandial blood glucose and both of serum cholesterol, and serum triglyceride. A negative statistically non-significant correlation was found between serum Hcy and both of total serum testosterone and serum prolactin.

The current study confirmed that Hcy is significantly associated with ED, especially moderate and severe grades. A highly significant negative correlation between serum Hcy level and IIEF-5 score was found. Moreover, higher serum Hcy level was shown as independent predictor of ED severity. There was highly significant positive correlation between serum Hcy level and mild to moderate, moderate, and severe ED ( $p < 0.001$ ).

Serum Hcy showed a weak statistically non-significant positive correlation ( $p > 0.05$ ) with EDV and a highly significant negative correlation ( $p < 0.001$ ) with RI of cavernosal artery highlighting a possible dose-dependence of Hcy levels in vascular function impairments of cavernous tissue.

Serum Hcy level was a statistically significant predictor of IIEF-5 score with 56.3 % of IIEF-5 can be predicted by serum Hcy with the following prediction equation ( $\text{IIEF-5} = 24.237 - 0.329 \times \text{serum Hcy}$ ). IIEF-5 score decreased 0.329 for each  $\mu\text{mol/l}$  of serum Hcy. The relationship between serum Hcy and ED based on the severity degree of ED was further confirmed in the logistic regression analysis ( $p < 0.001$ ).

Logistic regression analysis was performed to discover the potential association between Hcy, BMI, triglycerides, RI, along with the order of severity of ED. The logistic regression analysis revealed that BMI ( $p = 0.036$ ), triglycerides ( $p = 0.014$ ), Hcy ( $p < 0.001$ ) and RI ( $p < 0.003$ ) were significant predictor risk factors for ED. Higher serum Hcy level was shown as independent predictor of ED severity.

Serum Hcy showed high accuracy and a statistically significant diagnostic value for ED. Receiver operating characteristic (ROC) curve of serum Hcy was conducted to evaluate the sensitivity and specificity of serum Hcy as a diagnostic index for ED. Serum Hcy showed high accuracy AUC (AUC= 0.885). There was a statistically significant diagnostic value compared to the AUC/ROC value of 0.5 ( $p < 0.001$ ). At best cut off value of 8.28  $\mu\text{mol/L}$ , Hcy was able to predict ED with 90% sensitivity, 78% specificity, positive predicative value of 71.1 %, negative predicative value of 92.9 %, and accuracy of 82.5 %.

Several plasma Hcy concentration cut-off values have been established to discriminate between ED and control cases. **Demir et al.** (5) identified 12.1  $\mu\text{mol/L}$  as a cut-off value by performing the ROC curve analysis. **Al-**

**Hunayan et al.** (21) defined hyperhomocysteinemia in diabetic men with ED as plasma Hcy concentration over 14.3  $\mu\text{mol/L}$ . **Basar et al.** (24) adopted 12  $\mu\text{mol/L}$ , which was the median value of the ED patients' group, as the threshold value.

Despite the strong association between serum Hcy levels and ED, the question remains whether Hcy represents only a biomarker or a true cardiovascular risk factor. Therefore, it is still a matter of debate whether the correction of hyperhomocysteinemia can bring about a reduction in the incidence of ED and cardiovascular events. Unlike other risk factors, hyperhomocysteinemia is readily modifiable in most individuals by adjusting their diet or taking folate supplements (25). Because plasma Hcy level is a continuous biochemical variable, normality is difficult to define. Hyperhomocysteinemia is usually defined as an Hcy level in the 90th or 95th percentile of a control population, which in most studies is approximately 15  $\mu\text{mol/L}$  (26). However; in high-risk patients, such as those with personal or family history of premature cardiovascular disease, this may be too high. American Heart Association recommends a level of 10  $\mu\text{mol/L}$  as a therapeutic target to prevent increased risk of vascular endothelial dysfunction (3). Furthermore, a "target" concentration of Hcy-lowering treatment of about 13–15  $\mu\text{mol/L}$  is proposed by a European expert panel for patients with coronary vascular disease (27).

The available data on the efficiency of Hcy-lowering therapy using folic acid or vitamin B in the treatment of ED are scanty. Mild and moderate hyperhomocysteinemia, defined as serum Hcy levels  $< 100 \mu\text{mol/L}$ , can be corrected with folic acid and vitamin B supplementation (28). Although a threshold value of Hcy levels was identified using ROC method, the targeting Hcy levels of ED patients were not established. The optimal treatment strategy for ED patients with high Hcy concentration on the basis of folic acid and vitamin B or alternatively PDE5 inhibitors and testosterone needs further studies. Idiopathic vasculogenic ED patients showed improvement in the severity of ED and a significant decrease in peripheral and penile Hcy plasma levels after folic acid therapy (19).

## CONCLUSIONS

- Increased levels of serum Hcy are more often observed in subjects with ED.
- Elevated Hcy is associated with ED and may represent an important risk factor and play a pathophysiologic role in ED. Hence, Hcy-lowering agents, such as folic acid and vitamin B<sub>12</sub>, seem reasonable choices for the prevention and management of this condition.
- ED has a graded response to increased levels of Hcy, and there was a positive correlation between Hcy and ED.
- The current study supports a potential role for Hcy in the diagnosis and target treatment in patients with early ED. The correction of this marker may

represent a future target for monitoring efficacy of ED therapy.

## RECOMMENDATIONS

- Measurement of Hcy in the general population to screen for ED risk is not recommended.
- Measurement of Hcy should be considered in clinical and epidemiologic studies on ED when the conventional risk factors are being assessed.
- In young ED patients (< 40 years), Hcy should be measured to exclude homocystinuria.
- Erectile dysfunction patients with Hcy >15 µmol/L belong to a high-risk group. It is especially important for them to follow a healthy lifestyle and to receive optimal treatments for known causal risk factors. A high Hcy concentration should be used as a prognostic factor for CVD events and mortality.

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