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Low serum folic acid can be a potential independent risk factor for erectile dysfunction: a prospective case–control study

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Abstract

Purpose The purpose of the study was to compare serum level of folic acid (FA) in patients with erectile dysfunction (ED) versus healthy controls and to assess its correlation with other well-known confounders for ED.

Methods Our prospective study compared FA in 60 patients with ED versus 30 healthy controls. Patients were excluded if they had any hormonal disorders, Peyronie's disease, or decompensated systemic illnesses. ED was evaluated by the validated Arabic version of the abbreviated five-item form of the International Index Of Erectile Function and confirmed by penile duplex. Serum FA level was assayed using ELIZA. Mann–Whitney, Kruskal–Wallis, and Chi-square tests and Spearman correlation were used as appropriate and confirmed by logistic regression model.

Results Our study revealed that the median FA of the cases and the controls were 7.1 ng/mL and 13.4 ng/mL, respectively, and this difference was of high statistical significance ($p < 0.001$). Moreover, our study demonstrated significant relations between serum FA with DM, HTN, smoking, age, and cholesterol (p 0.01, 0.03, 0.014, 0.001, and 0.015, respectively). Our study showed that the best cut-off point of serum FA to detect patients with ED was found to be ≤ 9.42 with sensitivity of 80.00%, specificity of 93.33% and area under curve (AUC) of 91.3%.

Conclusion Serum FA level decreased as the severity of ED increased even after adjustment of age, serum testosterone, DM, HTN, and smoking. FA deficiency might be an independent risk factor of ED.

Keywords Erectile dysfunction · IIEF-5 · Serum folic acid · Severity of erectile dysfunction

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain or maintain an erection sufficient to permit satisfactory sexual performance [1]. ED is a major component of male sexual dysfunction which negatively affects the quality of life for millions of men worldwide [2]. The pathophysiology of ED includes vasculogenic, neurogenic, hormonal, anatomical, drug-induced, and psychogenic causes [3]. Penile erection is a vascular event that requires an intact endothelium and vascular smooth muscles of the corpus cavernosum. The pathogenesis of both endothelial dysfunction and ED are linked through decreased expression and activation of endothelial nitric oxide synthase (NOS) which is responsible for the formation of nitric oxide (NO) which is a relaxing factor that plays a major role in activation and maintenance of the erection process [4]. Homocysteine (Hcy) is a potent NOS inhibitor as it promotes NOS uncoupling reducing the production of the endothelial NO [5]. Hyperhomocysteinemia was recently reported to be a novel ED risk factor [6]. Folic acid (FA) plays an important role in the metabolism of NO and homocysteine as it promotes the remethylation of homocysteine (Hcy) to methionine (Met) and inverts NOS uncoupling. On the contrary, FA deficiency prevents remethylation of homocysteine and permits its accumulation which induces endothelial dysfunction [7]. Recently, Hamidi Madani et al. [8] demonstrated that

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FA supplementation improves ED, together with dramatic improvement in the IIEF scores in diabetic patients with ED who received combined tadalafil and FA than those who received tadalafil only for 3 months [8]. Moreover, many reports showed that FA supplementation improves endothelial dysfunction in patients with diabetes mellitus (DM) or hypertension [9].

Thus, FA is supposedly to have an essential role in proper erection mechanism, and FA supplementation might be used in the treatment of ED. We aimed in this prospective study to evaluate the serum FA levels of patients with different degrees of ED and compare it to those of healthy controls. In addition, we aimed to unravel the correlation between serum FA and other well-known confounders for ED to reveal whether low serum FA can be a potential independent risk factor for ED.

Methods

Study design and participants

This prospective study has been carried out on 90 individuals who were recruited from our department from March 2017 to August 2018 and were divided into two groups, group (1) were 60 married males complaining of ED and group (2) were 30 married healthy controls. All the participants signed an informed consent before enrollment to this study that was followed by approval of the local review board which conforms to Helsinki declaration 1964.

All the participants were subjected to the following

Detailed personal history and past history in the form of History of any medical diseases that may be a risk factor for ED, particularly DM, hypertension, coronary heart disease, and liver or kidney and neurological disorders were evaluated. History of pelvic trauma or pelvic surgery, in addition to history of drug intake especially those affecting sexual function were also evaluated. The presence of factors that may precipitate psychogenic ED such as anxiety, depression, phobia, or history of any psychic disorders were assessed. Furthermore, they were subjected to penoscrotal examination in which the penis was inspected for the size and site of the urethral meatus and is palpated for tenderness or plaques.

In addition, they were subjected to general examination to exclude any decompensated systemic illness as mentioned above. Patients with penile deviation, Peyronie's disease, or penile fibrosis were excluded from the study. All the participants were evaluated by the Arabic version of the International Index of Erectile Function (IIEF-5) Questionnaire which is a self-administered questionnaire and has been demonstrated to have a high degree of sensitivity and specificity to ED [3, 10]. Besides, the severity of ED was partitioned into five grades: no ED total score (22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), and severe ED (1–7). Patients with a score of 21 or less may have evidence of ED [11]. Also, the diagnosis of ED was confirmed by penile duplex where the patients were given 0.25 cc Quadmix. Consequently, all the participants with poor response to the Quadmix, together with either decreased peak systolic velocity and/or increased end diastolic velocity were classified into arteriogenic, veno-occlusive dysfunction or mixed ED, respectively. Eventually, all the participants were studied between 8 and 10 am after a 12-h overnight fasting where venous blood was sampled for measurement of serum total testosterone (TT), serum prolactin, lipid profile, HbA1c, liver enzymes, urea, creatinine, and finally serum FA.

Inclusion criteria of the patients

Married men aged 30 years old or more and complaining of ED for 6 months at least.

Exclusion criteria of the patients

All patients with significant cardiac diseases (severe decompensated heart failure, unstable angina, and myocardial infarction), neurological diseases (multiple sclerosis, parkinsonism, cerebral stroke, CNS tumors, spinal cord injury, spinal cord diseases and CNS operations), major psychiatric disorders (e.g. depression and anxiety), thyroid diseases, renal insufficiency, hepatic insufficiency, past history of pelvic trauma or pelvic surgery were excluded from the study.

In addition, patients with past history of penile fracture and penile operations, dyslipidemia (cholesterol > 200 mg/dl and/or TG > 150 mg/dl), hormonal imbalances such as hypogonadism (serum total testosterone (TT) < 2 ng/mL) or hyperprolactinemia (serum prolactin level > 35 ng/mL) or those who used drugs that affect sexual function or sexual desire such as selective serotonin reuptake inhibitors (SSRI) & tricyclic antidepressants, sedatives (benzodiazepines), anti-psychotic drugs, anti-epileptic drugs (tegretol), or finally drug abusers (opioids, marijuana, cocaine) were also excluded from the study.

Inclusion criteria of the controls

They were age-matched healthy controls who complain of testicular pain or scrotal swelling Serum FA measurement.

Fasting serum FA levels were measured using Enzyme-linked Immunosorbent Assay (ELISA) kit for FA (CEA610Ge, USCN Life Science Inc. Wuhan-China). The

normal range of serum FA measured is (5–15 ng/mL). All reagents, samples, and standards were prepared and 50 µL standard or sample was added to each well followed by the addition of 50 µL Detection Reagent A, with shaking and mixing followed by incubation for 1 h at 37 °C. Aspiration and washing were done three times on (Biotek washer instrument, USA sn: 233,397). 100 µL Detection Reagent B was added and incubated for 30 min at 37 °C followed by Aspiration and washing for five times. 90 µL Substrate Solution was added and incubated for 15–25 min at 37 °C, and finally 50 L Stop Solution was added. Reading was done immediately at 450 nm wavelength at (Biotek reader, USA sn: 233,754).

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 18.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The mean and standard deviation (SD) were calculated as follows

$$\text{Mean}\,(X) = \frac{\sum Xi}{n}$$

$$\text{SD} = \frac{\sum (X - Xi)^2}{n - 1},$$

where Σ is sum, (Xi) is each value in the series, and n is number of values in the series.

Independent-samples t test of significance was used when comparing between two means. Pearson's correlation coefficient (r) test was used for correlating data. Finally, receiver operating characteristic (ROC) curve was used to find out the overall predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cutoff value.

Results

Our prospective study demonstrated that the mean ages of the patients were higher than the controls. This difference was of a high statistical significance (Table 1). The mean total testosterone of the cases was lower than the controls. This difference was also of high statistical significance (Table 1). Additionally, the mean Glycosylated Hemoglobin A1C (HbA1C) of the cases was higher than the controls that was of statistical significance (Table 1). Furthermore, our study revealed that the median FA of the cases was significantly lower than the controls and this difference was of high statistical significance (Table 1). Also, our study demonstrated that the majority of the patients were diabetics and hypertensives and smokers (average cigarettes consumption = 365 packs/year), while two controls only were suffering from diabetes and hypertension. This difference was of high statistical significance (p 0.034, 0.002, respectively). Moreover, our study demonstrated significant relations between serum FA with DM and HTN and smoking (Table 2). Besides, our study revealed significant relations between the severity of ED with HTN and smoking in the patients group (Table 3). Our study revealed significant relations between the severity of ED with age and HTN and smoking and serum FA (Table 4). In addition, there were significant negative correlations between age and serum cholesterol and HbA1C with serum FA (Table 5). Further, our study showed that the best cut-off point of serum FA to detect patients with ED was found to be ≤9.42 with sensitivity of 80.00%, specificity of 93.33%, and area under curve (AUC) of 91.3%. Eventually, after adjustment of DM and HTN and smoking and age and serum testosterone, serum FA revealed significant relation with ED (Table 6).

Discussion

In this study, we have evaluated serum FA level in ED patients with different severities which were evaluated by IIEF-5 scores. We found 27 patients with risk factors for ED and 33 patients without risk factors. Interestingly, our study revealed that there was a statistical significant difference between patients with and without risk factors when compared to controls as regard serum FA. Thus, FA deficiency can be considered an independent risk factor for ED. Similarly, a study conducted by Yan et al. [7] that was one of the first to determine the relation between FA level and sexual dysfunctions, showed that serum FA levels were significantly lower in patients with ED than in healthy men [7]. Another study investigated serum FA levels in 120 patients complaining of ED of different severities and 40 healthy men served as controls. This study showed that the mean serum FA concentrations were significantly higher in the control group than in the severe and moderate ED groups [12]. Further, our study demonstrated a significant association between age and ED. In the same context, a study was done on 1402 men to assess the association between ED severity and long-term risk of coronary artery disease (CAD) and role of age as a modifier of this association [13]. They found that ED is more likely to develop among older men and age was the strongest predictor of ED [13]. Also, it

Table 1 Sociodemographic characteristics and laboratory findings of the patients and the controls

	Control group No. = 30	Patients group No. = 60	Test value	*p*-Value
Age				
Mean ± SD	34.13 ± 6.36	54.00 ± 9.73	− 10.134	< 0.001
Range	23–47	31–70		
Height				
Mean ± SD	174.27 ± 6.02	173.58 ± 4.83	0.582	0.562
Range	165–187	163–185		
Weight				
Mean ± SD	88.07 ± 8.45	90.17 ± 11.23	− 0.903	0.369
Range	74–105	70–124		
Total testosterone				
Mean ± SD	5.83 ± 2.07	4.10 ± 1.66	4.263	< 0.001
Range	3.02–13.45	2.02–12.44		
Serum cholesterol				
Mean ± SD	152.13 ± 44.75	146.17 ± 31.50	0.733	0.465
Range	62–245	74–195		
Serum triglycerides				
Mean ± SD	120.20 ± 37.65	107.66 ± 26.52	1.831	0.071
Range	64–196	62–153		
Glycosylated hemoglobin A1C (HbA1C)				
Mean ± SD	5.32 ± 0.33	5.92 ± 1.58	− 2.068	0.042
Range	4.8–6.01	4.75–12.46		
BMI				
Mean ± SD	29.06 ± 3.58	29.92 ± 3.59	− 1.076	0.285
Range	22.9–36.5	22.9–45.5		
Serum folic acid				
Median (IQR)	13.36 (10.88–14.24)	7.10 (5.42–8.75)	6.360	< 0.001
Range	4.09–15.97	2.57–12.21		

Table 2 The relation between serum folic acid and DM and HTN and smoking in the patients group

	Serum folic acid		Test value	*p*-Value
	Median (IQR)	Range		
DM				
Yes	5.45 (3.41–6.9)	3.11–7.78	2.569	0.010
No	7.47 (5.86–9.56)	2.57–12.21		
HTN				
Yes	6.35 (3.78–7.1)	3.11–12.15	2.185	0.029
No	7.48 (6.18–9.7)	2.57–12.21		
Smoking				
Yes	6.18 (3.48–7.35)	3.11–12.15	2.464	0.014
No	7.62 (6.23–9.7)	2.57–12.21		

should be noted that our study showed a significant negative correlation between age and serum FA. In the same vein, Neelam et al. [14] stated that elderly people may suffer from folate deficiency that may be related to aging, poor diet, malabsorption, drugs, or increased demand or be unexplained. Besides, our study showed a significant relation between serum FA and smoking [14].

Similarly, the study that was conducted by Constantine et al. [15] showed that serum FA levels were significantly lower in smokers compared to non-smokers as smoking has a significant impact on smokers' dietary habits, together with the chemical components that are found in tobacco smoke interact with folate and transform it into inactive compounds reducing its active concentration in biological fluids and possibly alter the ability of the cells to store and metabolize folate [15]. In addition, our study revealed a significant relation between serum FA and HTN. In the same line, Scazzone et al. [16] who assessed the levels of homocysteine (Hcy), vitamin B12, and folate in hypertensive patients in comparison to healthy controls found that homocysteine levels were significantly higher and FA levels were significantly lower in the hypertensive group in comparison

Table 3 The relation between the severity of ED and DM and HTN and smoking in the patients group

	Patients (60)						Test value	*p*-Value
	Mild (8)		Moderate (19)		Severe (33)			
	No.	%	No.	%	No.	%		
DM								
Yes	0	0.0	2	10.5	10	30.3	5.255	0.072
No	8	100.0	17	89.5	23	69.7		
HTN								
Yes	0	0.0	3	15.8	16	48.5	10.234	0.006
No	8	100.0	16	84.2	17	51.5		
Smoking								
Yes	1	12.5	3	15.8	17	51.5	8.819	0.012
No	7	87.5	16	84.2	16	48.5		

Table 4 The relation between sociodemographic characteristics and laboratory findings with the severity of ED among the patients

	Patients (60)			Test value	*p*-Value
	Mild (8)	Moderate (19)	Severe (33)		
Age					
Mean ± SD	42.00 ± 3.12	49.05 ± 8.88	59.76 ± 6.60	26.837	< 0.001
Range	37–45	31–68	39–70		
Height					
Mean ± SD	174.75 ± 4.80	174.21 ± 4.42	172.94 ± 5.10	0.678	0.512
Range	170–182	168–185	163–183		
Weight					
Mean ± SD	87.75 ± 5.34	90.16 ± 10.38	90.76 ± 12.80	0.225	0.799
Range	80–95	72–115	70–124		
Total testosterone					
Mean ± SD	5.07 ± 1.20	4.24 ± 1.22	3.79 ± 1.89	2.091	0.133
Range	2.8–6.98	2.4–6.8	2.02–12.44		
Serum cholesterol					
Mean ± SD	141.13 ± 44.77	135.11 ± 22.32	153.76 ± 31.18	2.333	0.106
Range	74–190	89–190	78–195		
Serum triglycerides					
Mean ± SD	98.50 ± 28.19	108.05 ± 24.16	109.65 ± 27.73	0.564	0.572
Range	62–142	71–147	65–153		
Glycosylated hemoglobin A1C (HbA1C)					
Mean ± SD	5.21 ± 0.39	5.46 ± 0.39	6.36 ± 2.01	3.110	0.052
Range	4.8–5.84	4.75–6.21	4.8–12.46		
BMI					
Mean ± SD	28.78 ± 2.17	29.67 ± 3.00	30.34 ± 4.14	0.674	0.514
Range	25.5–32.1	23–36.3	22.9–45.5		
Serum folic acid					
Median (IQR)	9.91 (9.48–10.84)	7.46 (6.49–7.96)	6.18 (3.78–7.48)	11.288	< 0.001
Range	8.81–11.34	4.46–11.39	2.57–12.21		

Table 5 Correlations between sociodemographic characteristics and laboratory findings of the patients and serum folic acid

	Serum folic acid	
	R	*p*-Value
Age	−0.411	0.001
Height	0.093	0.479
Weight	−0.019	0.886
BMI	−0.105	0.424
Total Testosterone	0.202	0.121
Serum Cholesterol	−0.313	0.015
Serum Triglycerides	−0.198	0.129
Glycosylated Hemoglobin A1C (HbA1C)	−0.332	0.010

to the controls [16]. Although we did not measure Hcy, yet, several studies evaluated the role of hyperHomocysteinemia (Hhcy) in ED. Boushey et al. [17] and Clarke et al. [18] revealed an association between HhCy and the risk of cardiovascular diseases [17, 18]. Consistently, Cheng et al. [19] demonstrated the involvement of Hhcy in endothelial dysfunction [19]. In 2017, a study conducted by Yang et al. demonstrated that Hhcy can be considered a novel risk factor for ED together with a connection between it and cardiovascular disease risk [6]. Further, Zhang et al. [20] showed that high Hcy level can be considered an independent risk factor for ED [20]. Interestingly, Sansone et al. [21] did not demonstrate a significant association between Hhcy and FA deficiency. However, their study revealed a significant association between ED, FA deficiency, and Hhcy. Thus, they concluded that FA deficiency may be an independent risk factor for ED [21].

Further, our study demonstrated a significant negative correlation between serum FA and serum cholesterol. This finding can be explained by increased low-density lipoprotein oxidation that is caused by high concentrations of Hcy which occurs in FA deficiency due to lack of remethylation of Hcy with subsequent Hcy accumulation [7, 22]. Moreover, a study conducted by Qin et al. [23] demonstrated that FA supplementation reduced the progress of atherosclerosis [23]. Finally, our study demonstrated a significant relation between serum FA and DM. Similarly, Ebesunun and Obajobi [24] showed that patients with Type 2 diabetes mellitus (T2DM) had increased plasma Hcy as well as decreased FA and vitamin B12 [24]. In fact, Hcy is a risk factor for cardiovascular events that is highly prevalent in diabetic people, and an indication of metabolic derangement [25]. Further, Feng et al. [26] demonstrated that higher serum level of Hcy both in Type 1 (T1DM) and in T2DM was observed by different studies especially in T1DM who are suffering from retinopathy and/or nephropathy [26]. On the other hand, a recent systematic review and meta analysis conducted by Sansone et al. [27] demonstrated a significant association between Hcy and ED [27]. Interestingly, this study revealed higher level of serum Hcy in non-diabetic versus diabetic ED patients [27]. However, such association was more evident among diabetic ED patients even for small changes in serum Hcy [27]. This finding could be explained by the fact that any small increase in serum Hcy will negatively affect erectile function in ED patients who suffer from other comorbidities as several risk factors act in a synergistic, rather than additive, fashion [28, 29]. Lastly, there were limitations of our study that must be acknowledged. One of the limitations of this study was the absence of enough information about the relationship between ED severity and Hcy level. Another limitation was the unequal splitting of the cases and the controls, together with small sample size.

Conclusion

In sum, a significant association between low serum FA level and ED severity was detected in the present study. Serum FA level decreased as the severity of ED increased even after adjustment of age, serum testosterone, DM, HTN, and smoking. Thus, FA deficiency might be an independent risk factor of ED.

Table 6 Multivariate logistic regression analysis for the relation between ED and serum folic acid after adjustment of DM and HTN and smoking and age and serum testosterone

	B	S.E.	Wald	*p*-Value	Odds ratio	95% CI for OR	
						Lower	Upper
DM	2.052	1.567	1.716	0.190	7.785	0.361	167.805
HTN	−1.362	1.506	0.817	0.366	0.256	0.013	4.908
Smoking	−0.355	1.015	0.122	0.727	0.701	0.096	5.127
Age	0.296	0.197	3.821	0.057	1.178	0.987	1.386
Serum testosterone	−0.313	0.334	1.370	0.534	0.870	0.407	1.863
Serum folic acid	−0.738	0.167	19.607	< 0.001	0.478	0.345	0.663

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local ethical committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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