Folic acid levels in erectile dysfunction patients

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Introduction
Erectile dysfunction (ED) is the persistent inability to achieve and maintain an erection to permit satisfactory sexual activity. This study aimed to evaluate the association between serum folic acid (FA) level and ED evaluated by International Index of Erection Function 5 score (IIEF-5 score) and penile duplex ultrasonography.

Patients and methods
The study included 30 ED patients and 30 persons as controls within the age group of 20–50 years. FA levels were measured using enzyme-linked immunosorbent assay for all patients and controls. All patients and controls were asked to complete the IIEF-5. ED patients underwent pharmacopenile duplex ultrasonography.

Results
There was statistically significant lower serum FA level in the patient group than control group. There was statistically significant positive correlation between serum FA levels and IIEF-5 scores. There was also statistically significant lower serum FA level among ED patients with arterial insufficiency, venous leakage, and mixed vascular affection than those with normal penile duplex; Also, there were lower serum FA level in patients with arterial insufficiency and mixed vascular affection than those with venous leakage patients.

Conclusion
A significant lower FA levels was detected in ED patients; FA level correlated positively with IIEF-5 score. FA levels were significantly lower in ED patients with vasculogenic affection detected by penile duplex ultrasound compared with ED patients without vasculogenic affection. FA supplementation is recommended in the treatment of ED.

Keywords:
erectile dysfunction, folic acid deficiency, penile duplex, vascular insufficiency

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Introduction

Erectile dysfunction (ED) affects 50% of men older than 40 years, exerting substantial effects on the quality of life. This common problem is complex and involves multiple pathways. Penile erections are produced by an integration of physiologic processes involving the central nervous, peripheral nervous, hormonal, and vascular systems. Any abnormality in these systems, whether from medication or disease, has a significant impact on the ability to develop and sustain an erection, ejaculate, and experience orgasm [1]. Folic acid (FA) is a water-soluble B vitamin that assists in human red blood cell maturation, and is the coenzyme that participates in the transfer and metabolism of a single carbon unit from homocysteine (Hcys) to methionine (Met) and is important for the synthesis of DNA, RNA, and neurotransmitters [2]. 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 is 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 the activation and maintenance of the erection process [3]. Homocysteine is a potent NOS inhibitor as it promotes NOS uncoupling reducing the production of the endothelial NO [3]. Hyperhomocysteinemia (HHcys) was recently reported to be a novel ED risk factor [3]. FA has been demonstrated to play an important role in the metabolism of NO and homocysteine by potentially inverting NOS uncoupling [4,5]. FA deficiency has been found to cause endothelial dysfunction and ultimately ED [6]. Also, FA deficiency decreases DNA methylation and impairs DNA repair, which result in genetic mutation or triggering of endothelial apoptosis [7]. To the best of our knowledge, no previous studies combined 5-item International Index of Erectile Function (IIEF-5) score and penile duplex ultrasonography in ED patients in the evaluation of FA levels. The aim of this study was to objectively

assess the serum FA level in ED patients evaluated by IIEF-5 score and penile duplex ultrasonography.

Patients and methods

The study included 30 ED patients and 30 healthy age-matched persons as controls attending the Andrology and Dermatology Outpatient Clinic, Assiut University Hospital, and all patients signed informed consent. IRB number is 17101038 and Assiut Faculty of Medicine approved the study. Inclusion criteria were: age 20–50 years, patients complaining of ED, able and willing to give written informed consent. The studied cases were subjected to history taking including age, duration of sexual dysfunction, smoking status, past medical history, and sexual history as morning erection. General examination included blood pressure and local examination of genital organs. All patients and controls were asked to complete the IIEF-5 questionnaire – Arabic version IIEF [8], which include items on frequency and a single item on intercourse satisfaction. Each item is scored from 0 to 5. Patients who report IIEF-5 score less than or equal to 21 were considered as having ED. ED patients underwent pharmacopenile duplex ultrasonography to investigate the etiology of ED either arterial insufficiency, venous leakage, or mixed vascular affection. Penile duplex sonography done by intracavernosal injection (ICI) of a pharmacostimulant of 1 ml of prostaglandin E1 was injected into one corpus cavernosum. Duplex sonography evaluation was performed with a color Doppler ultrasound machine (Esaote, S.P.A, Italy). Diagnostic criteria of duplex normal cavernosal artery diameter is 0.5 mm, peak systolic velocity (PSV) should be at least 25 cm/s, end-diastolic velocity (EDV) is less than 5 cm/s, resistance index (RI) equal to 1. In venous leakage patients EDV prolonged for more than 5 cm/s, RI less than 1. In arterial insufficiency patients PSV prolonged for more than 25 cm/s, RI less than 1, In mixed vasculogenic affection PSV is prolonged and EDV is more than 5 cm/s [9]. For assessment of serum FA level for all patients and controls, 2 ml blood was collected from 9 a.m.: 2 pm on plane tubes, left for 10 min to clot, and then centrifuged at 3000 rpm for 5 min. After centrifugation, serum was separated into aliquots, then stored at −20°C until assayed, detection range of the kit (1–20 mg/l), and measurements were made in the Clinical Pathology Department, Assiut University Hospital, by a single person who performed the assay blinded to the results of the questionnaire using enzyme-linked immunosorbent assay (SinoGeneClon Biotech Co. Ltd., Zhejiang, China) read by enzyme-linked immunosorbent assay plate reader (Stat fax 2100 plate reader, Virginia, USA).

Statistical analysis

Data entry and analysis were done using SPSS version 23 (Statistical Package for the Social Sciences). Data were presented as number (%) for nonparametric parameters or mean±SD for parametric parameters. χ^2 test and Fisher's exact test were used to compare qualitative variables. One-way analysis of variance test was used to compare quantitative variables. *P* value less than 0.05 was considered statistically significant.

Results

Demographic data of patients and controls

There were insignificant differences between patient and control groups about age, age of wife, residence and smoking, and BMI (Table 1).

Folic acid levels in patients and controls

There were statistically significant lower serum FA level in the patient group than the control group ($P < 0.01$) (Table 1).

IIEF-5 score in patients and controls

There were highly significant lower levels of IIEF-5 score in the patient group than the control group ($P < 0.000$) (Table 1).

Intracavernosal injection response in the patient group

Erectile response of patients after ICI of 1 ml prostaglandin E1 during penile duplex examination in the patient group, 33.33% had response E2 and 30.0% had response E3, 13.3% had response E4, and 16.7% had response E5.

Intracavernosal injection response and folic acid level in the patient group

There were statistically significant lower serum FA level in patients with abnormal ICI response (E1-3) compared with those with normal ICI response (E4-5) (Table 2).

Penile duplex results in the patient group

Among the patients, 30% have venous leakage, 20% have arterial insufficiency, and 20% have mixed vascular affection. On the other hand, 30% have normal penile duplex result (Table 3).

Penile duplex result in relation to folic acid level in the patient group

Patients with arterial insufficiency, venous leakage, and mixed vascular affection had significant lower serum FA

Table 1 Demographic data in patients and control groups

Items	Patient group (*n*=30)	Control group (*n*=30)	*P*
Age (years)	35.07±6.47	32.93±8.12	0.210
Age of wife	36.06±6.78	31.67±4.12	0.215
Residence [*n* (%)]	22 (73.3%)	20 (66.67)	0.372
Rural	8 (26.7)	10 (33.33)	0.275
Urban	14 (46.7)	15 (50)	0.30
Smoking [*n* (%)]			
No	16 (53.3)	15 (50)	0.003
Yes	27.8±3.3	27.2	0.0005
BMI (weight/square height)			
Folic acid	4.95±2.80	6.69±2.48	
IIEF-5 score	15.56±2.97	24.00±0.94	

IIEF-5, International Index of Erection Function 5 score.

Table 2 Comparison between intracavernosal injection response and folic acid in the patient group

Item	Normal ICI response (4-5) 30%	Abnormal ICI response (1-3) 70%	*P*
Folic acid concentration (ml)	7.25±2.47	4.02±2.37	0.007

ICI, intracavernosal injection

Table 3 Penile duplex results of the patient group

Items	Patient group (*n*=30) [*n* (%)]
Conclusion	
Normal penile duplex	9 (30.0)
Arterial insufficiency	6 (20.0)
Venous leakage	9 (30.0)
Mixed vasculogenic	6 (20.0)

than those with normal penile duplex result ($P < 0.001$). Also, there were lower serum FA levels in patients with arterial insufficiency, mixed vascular affection than those with venous leakage ($P < 0.01$) (Table 4).

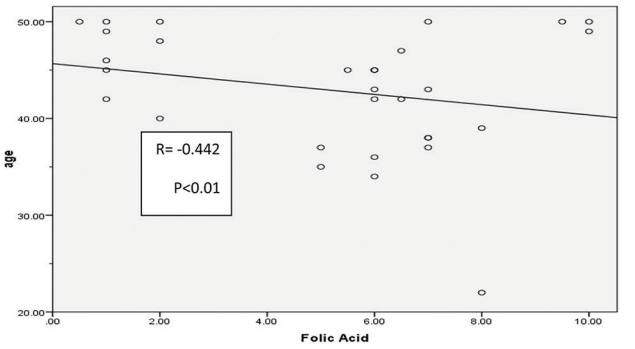
Correlation between folic acid level and other variables

There was statistically significant negative correlation between serum FA level and age of patient groups ($P < 0.01$) (Fig. 1). There was significant positive correlation between serum FA level and IIEF-5 score ($P < 0.01$) (Fig. 2).

Discussion

Penile erection is a vascular event that requires an intact endothelium; thus, the pathogenesis of both endothelial dysfunction and ED are intimately linked through decreased expression and activation of endothelial NO,NOS [10]. FA has been demonstrated to play an important role in the metabolism of NO by potentially inverting NOS uncoupling [4,5]. NO, plays a pivotal role in the activation and maintenance of the erection process, the best-characterized endothelium-derived relaxing factor [11,12]. The low serum FA level causes HHcys [13]. Accumulation of homocysteine has

Figure 1



Correlation between folic acid and age in the patient group

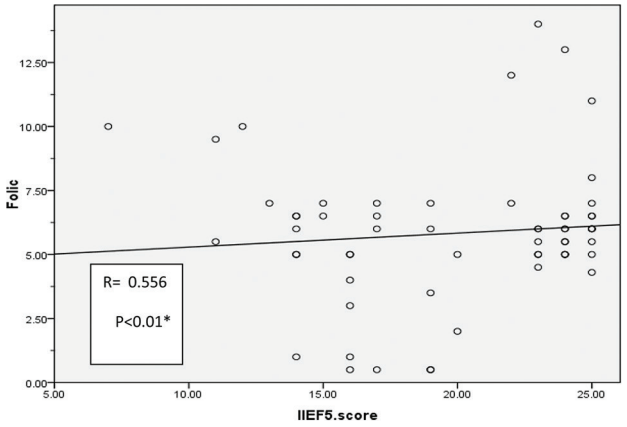
deleterious effects on vascular endothelial cells causing atherosclerosis [4]. The incidence of ED increase with age and its prevalence is very high, affecting up to 53.4% of men aged 30–80 years [14]. In the present study there was statistically significant negative correlation between serum FA levels and age of ED patients. This may be due to the effect of FA deficiency which induce ED, so ED prevalence increases with age; this agrees with Attia *et al.* [3] who showed significant negative correlations between age and serum FA. In contrast, Yan *et al.* [6] who showed no correlation coefficients of FA with age. In this study, there were statistically significant lower serum FA levels in the patient group than the control group. This agrees with Yan *et al.* [6] who showed that the FA level was significantly lower in patients with ED (with/without premature ejaculation) than in healthy men. Karabakan *et al.* [15] classified the patients with ED into those with severe, moderate, and mild ED according to the IIEF-5 score. The mean serum FA level was significantly lower in both severe and moderate ED groups than in the control group, but was not significantly lower in the mild ED group than in the control group. Also, this agrees with [3] Attia *et al.* who showed that FA of the ED cases significantly lower than controls and this difference is of high statistical significance. The IIEF-5 score is one of the most commonly used validated instruments for the evaluation of ED severity which has high sensitivity and specificity for detecting treatment effects. In this study, there were highly significant lower IIEF-5 score in ED patients than the control group. This agrees with Karabakan *et al.* [15] and Sansone *et al.* [16] who reported significant lower IIEF-5 score in the patient group than the control group. In the present study, there was statistically significant positive correlation between serum FA levels and IIEF-5 scores; this agrees with [6] Yan *et al.* who showed that there is a positive correlation between serum FA and IIEF-5 score and intravaginal ejaculation latency time and this was due to the effect of FA on the nitric oxide metabolism, 5-hydroxytryptamine, and homocysteine. Penile duplex

Table 4 Folic acid levels in different penile duplex results

Items	Normal penile	Arterial	Venous	Mixed	*P*	P_1	P_2	P_3	P_4	P_5	P_6
Folic acid (ml)	7.08±1.53	4.05±3.18	5.58±2.90	4.00±2.43	0.0008**	0.0293	0.0082	0.0012	0.0061	0.0381	0.375 (NS)

P_1, *P* (normal vs arterial); P_2, *P* (normal vs venous); P_3, *P* (normal vs mixed); P_4, *P* (arterial vs venous); P_5, *P* (venous vs mixed); P_6, *P* (arterial vs mixed).

Figure 2



Correlation between folic acid and International Index of Erection Function 5 score in patient groups.

ultrasonography which combines ICI with Doppler ultrasound to evaluate blood flow direction and velocity is the most common and informative method of assessing both arterial insufficiency and veno-occlusive dysfunction [17]. To the best of our knowledge, no previous studies combined IIEF-5 score and penile duplex ultrasonography in ED patients in the evaluation of FA levels. There were statistically significant lower serum FA levels in patients with abnormal (E1-3) ICI response than those with normal (E4-5) ICI response. There was statistically significant lower serum FA level among patients with arterial insufficiency, venous leakage, and mixed vascular affection than those with normal penile duplex result. Also, there were lower serum FA levels in patients with arterial insufficiency and mixed vascular affection than those with venous leakage patients. In another study which showed the relationship of h HHcys and ED using penile Doppler ultrasound, a significant association with impaired flow-mediated vasodilatation and vascular abnormalities in patients with HHcys was seen [18]. Also in the study by Sansone *et al*. [16] no significant correlation was observed between homocysteine and FA in the patient group. In conculsion, FA plays an important role in male sexual function and FA supplementation may provide potential therapeutic advantage for men with ED.

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Conflicts of interest

There are no conflicts of interest.

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