

Sexual Dysfunction

Serum High-Sensitivity C-Reactive Protein Levels and Response to 5 mg Tadalafil Once Daily in Patients With Erectile Dysfunction and Diabetes

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Purpose: We studied the relative importance of high-sensitivity C-reactive protein (hs-CRP) concentrations in patients with erectile dysfunction (ED) and diabetes and determined whether the hs-CRP level predicts the response to treatment with 5 mg tadalafil once daily.

Materials and Methods: We enrolled 102 men (aged 40–60 years) with diabetes and ED. All patients completed the International Index of Erectile Function (IIEF) questionnaire and were given 5 mg tadalafil daily. The IIEF and serum hs-CRP levels in patients and healthy controls and in patient responders and nonresponders to 5 mg tadalafil once daily were compared.

Results: Median age was 53.2 years (range, 45 to 62 years) in patients and 55.6 years (range, 47 to 64 years) in healthy controls ($p=0.158$). The median duration of diabetes was 54.3 months (range, 34 to 70 months). The median IIEF and hs-CRP level were 12.1 (range, 5 to 20) and 0.21 mg/dL (range, 0.05 to 0.6 mg/dL) in patients and 28.2 (range, 13 to 31) and 0.09 mg/dL (range, 0.04 to 0.2 mg/dL) in the controls, respectively ($p_{\text{IIEF}}=0.000$, $p_{\text{CRP}}=0.031$). After tadalafil treatment, 71 patients (69.6%) achieved an erection sufficient for sexual intercourse, whereas 31 (30.4%) did not. The median age of the tadalafil nonresponders was 56.2 years (range, 45 to 64 years) and that of the responders was 51.3 years (range, 42 to 62 years; $p=0.065$). Median hs-CRP levels were 0.31 mg/dL (range, 0.18 to 0.62 mg/dL) in nonresponders and 0.14 mg/dL (range, 0.09 to 0.4 mg/dL) in responders, respectively ($p=0.028$).

Conclusions: Serum hs-CRP was significantly higher in patients with ED and diabetes mellitus than in patients without ED. A significant correlation was observed between serum hs-CRP levels, the degree of ED, and responsiveness to tadalafil.

Keywords: C-reactive protein; Diabetes mellitus; Erectile dysfunction; Phosphodiesterase 5 inhibitors

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INTRODUCTION

Diabetes mellitus (DM) represents a major risk factor for erectile dysfunction (ED). The prevalence of ED is significantly greater in men with DM, and the onset of ED generally occurs at an earlier age in men with DM than in men in the general population [1]. ED is positively correlated

with the duration and severity of DM and poor glycemic control [1]. Although the etiology of DM-induced ED is multifactorial and still unknown, endothelial dysfunction is thought to be one of the key factors. Patients with DM and ED often have severe endothelial dysfunction and respond poorly to oral phosphodiesterase (PDE)5 inhibitors [2]. Tadalafil is a PDE5 inhibitor that is safe and efficacious for

treating ED across a variety of clinical populations, including patients with many risk factors [3]. Generally, administration of PDE5 inhibitors results in a greater than 70% success rate in patients with ED [3]. However, the response rate to PDE5 inhibitors in patients with DM and ED ranges from 51% to 59% [4], which can be explained by decreased endothelial function. ED in men with DM is associated with diabetic neuropathy, peripheral vascular disease, poor glycemic control, use of specific types of medications, and increased age [4]. Either significant autonomic neuropathy or endothelial dysfunction would be expected to reduce the efficacy of a PDE5 inhibitor [5]. Of course, the usual causes of ED in the general population, such as depression, recent surgery, hypertension, and hyperlipidemia, may also play a role in patients with DM [6]. All of these factors need to be considered when treating ED in this population. Serum high-sensitivity C-reactive protein (hs-CRP) levels increase with the severity of preeclampsia, reflecting endothelial dysfunction. High-sensitivity CRP is an acute-phase protein that is mainly synthesized in the liver and can be used as a marker of bacteremia or sepsis and may also predict the outcome of these infections [7]. High-sensitivity CRP may also be elevated with trauma, surgery, burns, tissue necrosis, and advanced cancer and is a marker of adverse outcomes from acute coronary syndromes and atherosclerosis [7]. High-sensitivity CRP is a systemic inflammatory and cardiovascular biomarker that is associated with endothelial dysfunction and metabolic syndrome. Impaired endothelial dysfunction is associated with increased plasma concentrations of inflammatory markers, and both may play a role in the etiopathogenesis of peripheral arterial disease.

ED is a manifestation of endothelial dysfunction and is part of a spectrum of atherosclerotic diseases that culminate in arterial insufficiency. Some evidence suggests an association between hs-CRP levels and ED severity. Thus, we evaluated the relative importance of the hs-CRP level in patients with ED and DM and determined whether there was a difference in hs-CRP level according to the response to treatment with 5 mg tadalafil once daily.

MATERIALS AND METHODS

1. Subjects

A total of 102 men (age, 40 to 60 years) with ED and DM were enrolled between February 2010 and July 2012. A retrospective study was performed by reviewing the medical records of the patients. The control group contained 88 healthy subjects of similar ages without ED. The control group included patients who visited the clinic for benign prostatic hypertrophy (BPH) as the chief complaint, not ED. The criteria for exclusion were the presence of any active inflammatory diseases at the time of measuring the hs-CRP level, the use of immune suppressants, a history of malignant neoplasms, or a history of chronic inflammatory diseases, such as arthritis, lupus, or inflammatory bowel disease. The treatment group was given 5 mg tadalafil

once daily for 12 weeks. Collection and analyses of all samples were approved by the Institutional Review Board of Pusan National University Hospital, Busan city, Republic of Korea.

2. Clinical parameters

We evaluated the responses to the International Index of Erectile Function (IIEF) Q3 and Q4 questionnaires, the IIEF-erectile function (IIEF-EF) domain, and the Global Efficacy Assessment questionnaire (GEAQ), as well as serum hs-CRP levels before and after treatment. Medical history (hypertension, hepatic disease, central nervous system disorder, DM, dyslipidemia, and other endocrine and metabolic disorders) and smoking history were evaluated. All patients with ED underwent a penile color Doppler ultrasound examination after intracavernous injection of alprostadil (10 µg).

3. Serum hs-CRP measurement

Blood was collected to measure hs-CRP. Serum samples for hs-CRP levels were stored at -80°C until assayed. Serum hs-CRP levels were measured by using a high-sensitivity immunoturbidimetric method.

4. Statistical analysis

Continuous data were reported as medians and the interquartile range (IQR). All statistical analyses were performed by using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA), and $p < 0.05$ was considered significant by using the nonparametric Mann-Whitney U test (continuous variables in Tables 1 and 2), chi-square test (categorical variables in Tables 1, 2), Wilcoxon signed-ranks test (Fig. 1), Kruskal-Wallis test (Fig. 2), and simple linear regression test (Fig. 3).

RESULTS

1. Patient characteristics

The median (IQR) age of the 102 patients with DM and ED was 53.2 years (45 to 62 years). The control group patients had a median (IQR) age of 55.6 years (47 to 64 years). The median (IQR) duration of ED was 38.9 months (12 to 60 months). The median (IQR) of the IIEF-EF score was 12.1 (5 to 20) compared with 28.2 (13 to 31) in the ED with DM group and the non-ED group, respectively. In the ED with DM group, the severity of ED according to the IIEF-EF domain score was severe (< 11) in 30 patients (29.4%), moderate (11 to 16) in 51 patients (50%), mild to moderate (17 to 21) in 19 patients (18.6%), and mild (22 to 25) in 2 patients (2.0%). The median (IQR) duration of diabetes was 54.3 months (34 to 70 months). The median (IQR) hs-CRP level was 0.21 mg/dL (0.05 to 0.6 mg/dL) compared with 0.09 mg/dL (0.04 to 0.2 mg/dL) in the ED with DM group and the non ED group, respectively ($p=0.031$) (Table 1).

2. IIEF Q3 and Q4

The mean baseline IIEF Q3 (vaginal penetration) score

TABLE 1. Baseline patient characteristics

Characteristic	ED/DM group (n=102)	Non-ED group (n=88)	p-value
Age (y)	53.2 (45.0–62.0)	55.6 (47.0–64.0)	0.158
Duration of ED (mo)	38.9 (12.0–60.0)	NA	
IIEF-EF score	12.1 (5.0–20.0)	28.2 (13.0–31.0)	0.000
Severity of ED-EF domain score		NA	
Severe (<11)	30 (29.4)		
Moderate (11–16)	51 (50.0)		
Mild to moderate (17–21)	19 (18.6)		
Mild (22–25)	2 (2.0)		
Medical history			
Hypertension	39 (38.2)	8 (9.1)	
Hepatic disease	12 (11.8)	3 (3.4)	
Central nervous system disorder	9 (8.8)	0 (0)	0.000
Diabetes	102 (100)	12 (13.6)	
Dyslipidemia	33 (32.4)	8 (9.1)	
Other endocrine and metabolic disorders	12 (11.8)	2 (2.3)	
Smoking history			
Current smoker	25 (24.5)	14 (15.9)	0.023
Nonsmoker or exsmoker	77 (75.5)	74 (84.1)	
Duration of DM (mo)	54.3 (34.0–70.0)	39.5 (28.0–50.0)	0.011
hs-CRP (mg/dL)	0.21 (0.05–0.60)	0.09 (0.04–0.20)	0.031

Values are presented as median (interquartile range) or number (%).

ED, erectile dysfunction; DM, diabetes mellitus; IIEF, International Index of Erectile Function; EF, erectile function; NA, not applicable; hs-CRP, high-sensitivity C-reactive protein.

TABLE 2. Comparison between tadalafil responders and nonresponders in patients with ED and DM

Characteristic	Responders (n=71)	Nonresponders (n=31)	p-value
Age (y)	51.3 (42.0–62.0)	56.2 (45.0–64.0)	0.065
Duration of ED (mo)	34.6 (24.0–48.0)	40.5 (27.0–52.0)	0.102
Severity of ED-EF domain score			
Severe (<11)	12 (16.9)	18 (58.1)	
Moderate (11–16)	39 (54.9)	12 (38.7)	0.143
Mild to moderate (17–21)	18 (25.4)	1 (3.2)	
Mild (22–25)	2 (2.8)	0 (0)	
Medical history			
Hypertension	30 (42.3)	9 (29.0)	
Hepatic disease	8 (11.3)	4 (12.9)	
Central nervous system disorder	5 (7.0)	4 (12.9)	0.001
Diabetes	71 (100)	31 (100)	
Dyslipidemia	16 (22.5)	15 (48.4)	
Other endocrine and metabolic disorder	7 (9.9)	5 (16.1)	
Smoking history			
Current smoker	15 (21.1)	10 (32.3)	0.078
Nonsmoker or exsmoker	56 (78.9)	21 (67.7)	
Duration of DM (mo)	49.5 (34.0–62.0)	61.2 (47.0–78.0)	0.002
PCDU			
PSV (cm/s)	20.9 (14.0–30.0)	16.9 (12.0–27.0)	0.035
EDV (cm/s)	5.4 (4.0–7.0)	7.2 (5.0–10.0)	
HbA1c distribution (%)			
<7	29 (40.8)	8 (25.8)	
7–9.5	33 (46.5)	14 (45.2)	0.041
>9.5	9 (12.7)	9 (29.0)	
hs-CRP (mg/dL)	0.14 (0.09–0.4)	0.31 (0.18–0.63)	0.028

Values are presented as median (interquartile range) or number (%).

ED, erectile dysfunction; DM, diabetes mellitus; EF, erectile function; PCDU, penile color Doppler ultrasound; PSV, peak systolic velocity; EDV, end-diastolic velocity; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein.

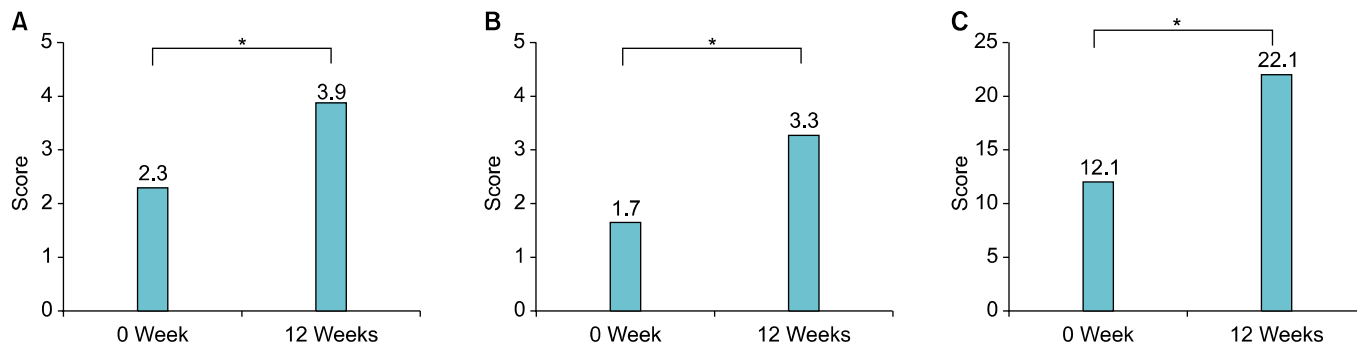


FIG. 1. Effects of tadalafil on responses to International Index of Erectile Function question 3 (During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?) (A) and question 4 (During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?) (B) 12 weeks after starting treatment. (C) Effects of tadalafil on the International Index of Erectile Function-Erectile Function domain score 12 weeks after starting treatment. * $p < 0.001$ vs. 0 week.

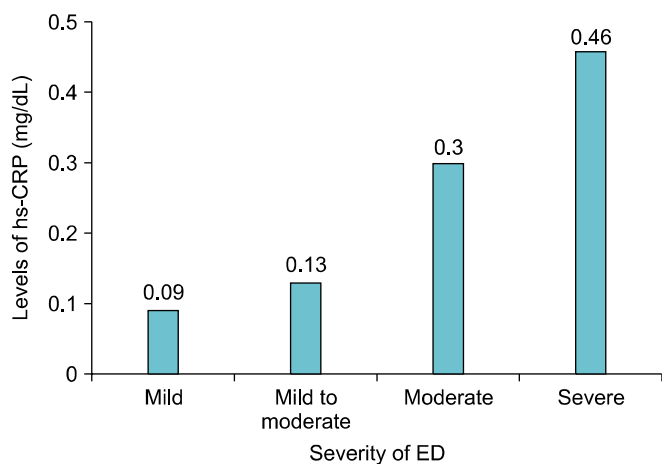


FIG. 2. Median hs-CRP levels according to erectile dysfunction severity ($p < 0.001$). hs-CRP, high-sensitivity C-reactive protein; ED, erectile dysfunction.

was 2.3 in the ED with DM group, but after the administration of 5 mg tadalafil daily, the 12-week mean score was 3.9 ($p < 0.001$) (Fig. 1). The mean baseline IIEF Q4 (maintenance of erection for intercourse completion) score was 1.7, but after the administration of 5 mg tadalafil daily for 12 weeks, the mean score increased to 3.3 ($p < 0.001$).

3. IIEF EF domain

The median (IQR) baseline IIEF EF domain score was 12.1 (5 to 20) in the ED with DM group (Fig. 1). After the administration of 5 mg tadalafil daily for 12 weeks, the median score increased to 22.1 ($p < 0.001$).

4. Treatment success rate

After 12 weeks, patients in the ED with DM group were questioned by use of the GEAQ. A total of 71 patients (69.6%) answered “yes” and 31 patients (30.4%) answered “no” to the question, “Did the 12-week treatment improve your erections?”

5. Comparison between tadalafil responders and nonresponders

Median (IQR) age was 56.2 years (45 to 64 years) and 51.3 years (42 to 62 years), respectively, in the tadalafil nonresponders and responders ($p = 0.065$). The median (IQR) durations of ED were 40.5 months (27 to 52 months) and 34.6 months (24 to 48 months) in nonresponders and responders, respectively ($p = 0.102$). Severity in the responders group on the basis of the ED-EF domain was severe (< 11) in 12 patients (16.9%), moderate (11 to 16) in 39 patients (54.9%), mild to moderate (17 to 21) in 18 patients (25.4%), and mild (22 to 25) in 2 patients (2.8%). In the nonresponders group, it was severe (< 11) in 18 patients (58.1%), moderate (11 to 16) in 12 patients (38.7%), mild to moderate (17 to 21) in 1 patient (3.2%), and mild (22 to 25) in 0 patients (0%) ($p = 0.143$). The median (IQR) duration of diabetes was 61.2 months (47 to 78 months) and 49.5 months (34 to 62 months) in nonresponders and responders, respectively ($p = 0.002$). Median (IQR) peak systolic velocity (PSV) was 20.9 cm/s (14 to 30 cm/s) in the responders and 16.9 cm/s (12 to 27 cm/s) in the nonresponders. Median (IQR) end-diastolic velocity (EDV) was 5.4 cm/s (4 to 7 cm/s) in the responders and 7.2 cm/s (5 to 10 cm/s) in the nonresponders ($p = 0.035$). Glycated hemoglobin (HbA1c) was $< 7\%$ in 29 patients (40.8%), 7% to 9.5% in 33 patients (46.5%), and $> 9.5\%$ in 9 patients (12.7%) in the responders group. In the nonresponders, the corresponding numbers of subjects were 8 (25.8%), 14 (45.2%), and 9 (29.0%), respectively ($p = 0.041$).

6. Levels of hs-CRP according to ED severity

Median hs-CRP levels according to ED severity were as follows: severe (< 11), 0.46 mg/dL; moderate (11 to 16), 0.30 mg/dL; mild to moderate (17 to 21), 0.13 mg/dL; and mild (22 to 25), 0.09 mg/dL ($p < 0.001$) (Fig. 2).

7. Levels of hs-CRP according to response to tadalafil

Median (IQR) hs-CRP levels were 0.31 ± 0.15 (0.18 to 0.63) and 0.14 mg/dL (0.09 to 0.40 mg/dL) in nonresponders and

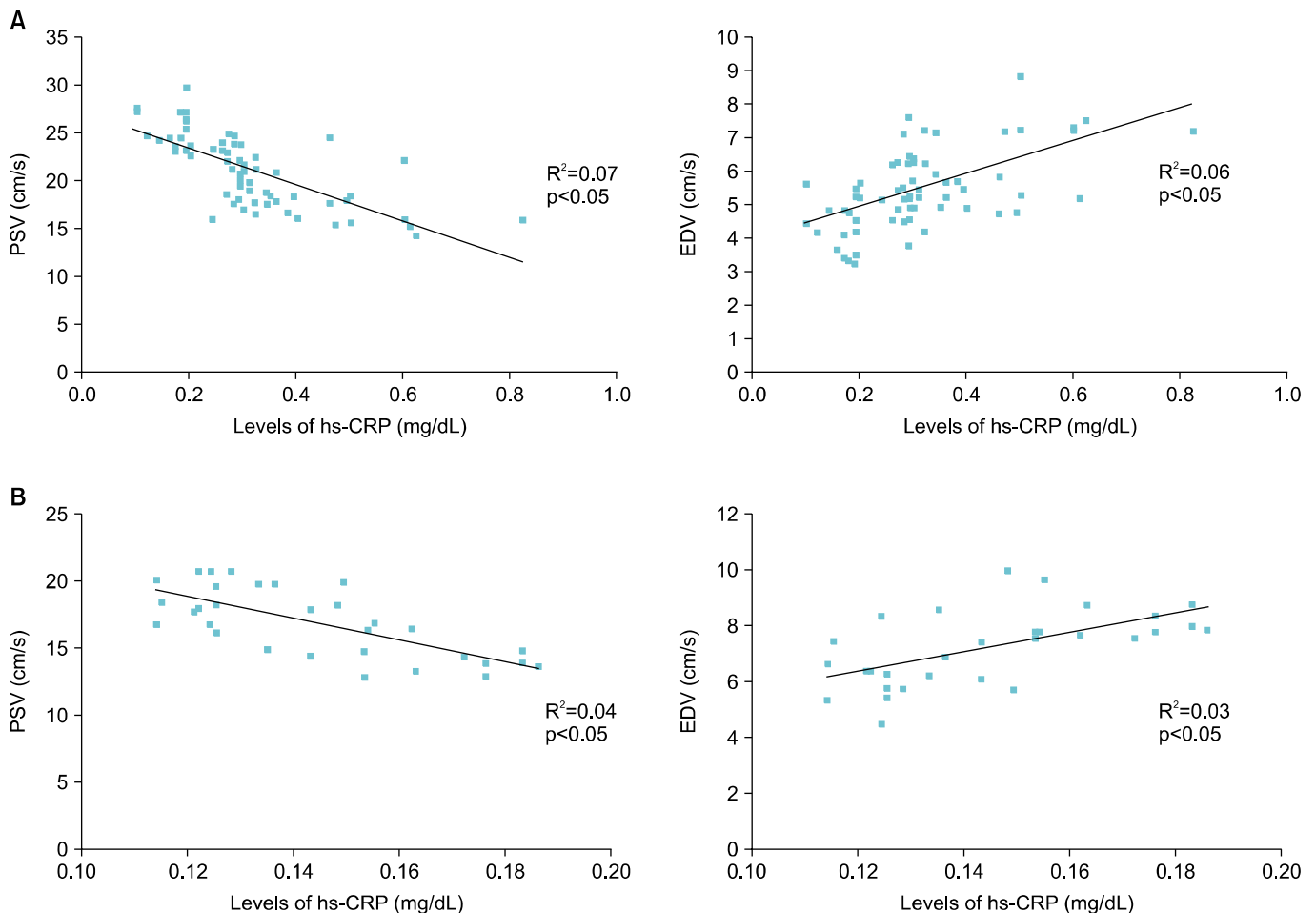


FIG. 3. Levels of hs-CRP and PCDU parameters. (A) Responders group, (B) nonresponders group. hs-CRP, high-sensitivity C-reactive protein; PCDU, penile color Doppler ultrasound; PSV, peak systolic velocity; EDV, end-diastolic velocity.

responders, respectively ($p=0.028$) (Table 2).

8. Levels of hs-CRP and penile color Doppler ultrasound parameters

Median (IQR) PSV was 20.9 cm/s (14 to 30 cm/s) in responders and 16.9 cm/s (12 to 27 cm/s) in nonresponders. Median (IQR) EDV was 5.4 cm/s (4 to 7 cm/s) in the responders group and 7.2 cm/s (5 to 10 cm/s) in the nonresponders group (Table 2). The PSV level decreased significantly with increasing hs-CRP level, whereas EDV increased significantly with increasing hs-CRP level (Fig. 3).

DISCUSSION

ED in men with DM has a multifactorial etiology that includes psychogenic factors, autonomic neuropathy, vascular disease, and drug intake. Several studies have demonstrated a high prevalence (35–75%) of ED in men with DM [4]. In patients with diabetes and hyperglycemia, the interaction between advanced glycation end products and advanced glycation end product receptors generates oxidative stress, vascular inflammation, and thrombosis, which contribute to vasculopathy [8].

PDE5 inhibitors are effective for treating ED regardless of its causative factors. However, PDE5 inhibitors are less efficacious in men with DM and ED than in patients with ED but without DM. Sildenafil, vardenafil, and tadalafil have been evaluated for ED in men with DM and have similar levels of efficacy, although head-to-head comparative studies have yet to be conducted [9].

In a study of men with ED and DM who received tadalafil once daily, mean IIEF-EF domain scores after 12 weeks of treatment were 18.3 (2.5 mg) and 17.2 (5 mg), respectively. The proportion of subjects with IIEF-EF domain scores ≥ 26 (normal erectile function) was 23.3% (2.5 mg) and 22.1% (5 mg) [10]. On-demand treatment with tadalafil in patients with DM improved ED by 58% and 60% for SEP2 and SEP3, respectively [11]. The Scheduled Use vs. On-demand Regimen Evaluation study in 14 European countries showed that $>40\%$ of patients with DM and ED had a normal IIEF-EF domain score (≥ 26), and the proportion of “yes” responses was 73% for SEP2 and $\geq 58\%$ for SEP3 after on-demand or three-times-per-week administration of 20 mg tadalafil [12]. In a multicenter study of 452 patients with type 1 and type 2 DM, 10 mg and 20 mg vardenafil improved erections in 57% and 72% of men, respectively [13].

Many studies have addressed the efficacy of sildenafil in men with diabetes and ED [4]. Although the response rate in that study was lower than that reported in nondiabetic patients, efficacy and overall patient satisfaction were high. However, another report suggested that the efficacy of sildenafil is negatively affected by factors such as poor control and long duration of DM, as well as by the presence of more than one diabetic complication [14].

In the present study, treatment with tadalafil did not alter mean HbA1c levels compared with baseline (data not shown). However, a difference in HbA1c level was observed according to responsiveness to tadalafil. These results are consistent with those of a meta-analysis of 12 placebo-controlled studies and a mirodenafil study in patients with types 1 and 2 DM [15].

The success rate in our study is similar to or slightly lower than that in previous studies. This may have been due to the duration of DM. The median (IQR) duration of DM in our study was 54.3 months (34 to 70 months) and that in the nonresponders group was 61.2 months (47 to 78 months). Furthermore, the duration was shorter in the responders group than in the nonresponders group. In a study by Goldstein et al. [13], the success rate was 75% but the mean duration of DM was only 12 months. The other reason for the lower success rate in our study could be the HbA1c levels. The median HbA1c level was 8.1% in our study: 8.7% in nonresponders and 7.9% in responders (data not shown). In Goldstein et al. [13], the mean HbA1c level was 7.35%±2.5%. In short, the longer duration of DM and higher mean HbA1c level may be reflected in the lower success rate of our study.

Bank et al. [16] showed that men with ED have increased levels of hs-CRP (2.6 mg/dL) and decreased endothelium-independent dilation (13.5%), both of which are subclinical markers of vascular disease. These data further support the hypothesis that ED is an early marker of systemic vascular disease and suggest that men with ED should undergo comprehensive cardiovascular screening and aggressive risk factor management.

Inflammatory markers such as hs-CRP and fibrinogen are independent risk factors and indicators for cardiovascular disease in various patient populations. An increased inflammatory status in men with ED is evident from the higher fibrinogen and hs-CRP concentrations [17].

Eaton et al. [18] compared endothelial function, coronary artery calcification, and hs-CRP in 70 subjects with ED from an endocrine clinic compared with corresponding values in 73 control subjects recruited by advertisement and found that subjects with ED had higher hs-CRP levels (2.62 mg/dL vs. 1.03 mg/dL), impaired flow-mediated dilation (2.36 mg/dL vs. 3.92 mg/dL), and more coronary artery calcification than did control subjects. Similarly, we found a significant correlation between hs-CRP levels and PSV and EDV results. A cardioprotective diet in men with metabolic syndrome and ED at baseline results in significant improvement in erectile and endothelial function, together

with a significant reduction in systemic vascular inflammation, as indicated by reduced levels of hs-CRP [8].

High-sensitivity CRP has been identified as another significant risk factor for ED. As a biomarker of inflammation, hs-CRP promotes endothelial dysfunction and plays a direct proatherogenic role [19]. We found that the level of hs-CRP was associated with responsiveness to tadalafil. Significantly elevated hs-CRP values (although within the normal range) are observed in young patients with ED, indicating that subclinical low-grade inflammation underlies ED pathogenesis and that young patients with ED have an increased probability of developing atherosclerotic diseases [19].

Several studies have shown that patients with ED have elevated CRP levels. However, there are between- and within-subject deviations in hs-CRP measurement [20, 21]. Some researchers have suggested that hs-CRP needs to increase or decrease by 120% to 175% before a change can be considered to have occurred. Therefore, it is necessary to collect each subject's blood samples on at least 10 occasions to sufficiently reduce intraindividual variation [21,22].

Although our study is the first to evaluate the association between hs-CRP levels and responsiveness to PDE5 inhibitors, the study did have several limitations. First, we did not conduct a multivariate analysis. Because hs-CRP is a nonspecific marker, bias from the differences in medical history between the groups could not be ruled out. Second, we had a relatively small sample size, and the results should be interpreted accordingly. A larger sample would have increased statistical power. Third, we collected each subject's blood samples only once at baseline. Thus, we could not clarify the within-subject deviation for hs-CRP measurement. Fourth, this study was retrospective, not prospective. Finally, the participants in the control group were patients with BPH and not completely healthy subjects.

CONCLUSIONS

Serum hs-CRP was significantly higher in patients with ED and DM than in patients without ED. We found a significant correlation between serum hs-CRP levels and the degree of ED and responsiveness to tadalafil. These results suggest that the serum hs-CRP level may be a marker for endothelial status in men with ED and DM.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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