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Effects of pioglitazone on erectile dysfunction in sildenafil poor-responders: A randomized, controlled study

Babak Gholamine, Massoumeh Shafiei, Manijeh Motevallian & Massoud Mahmoudian

Department of Pharmacology & Razi Institute for Drug Research, School of Medicine, Iran University of Medical Sciences.

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ABSTRACT

Purpose. The effects of pioglitazone on sildenafil responsiveness in men with erectile dysfunction (ED) and a history of poor response to sildenafil were assessed. **Methods**. In a double-blinded study, 38 men aged 47 ± 1.5 years with moderate-to-severe ED and poor response to sildenafil were randomly assigned to take a premedication of pioglitazone 30 mg (n=19) or placebo (n=19) once daily for 9 weeks along with on-demand use of sildenafil during the last month of pioglitazone-treatment. Erectile function (EF) scores, assessed by EF domain of International Index of Erectile Function (IIEF), along with responses to Global Assessment Questions (GAQs) were major outcome measures. Serum levels of total testosterone (T), dehydroepiandrosterone sulfate (DHEAS), glucose, lipid profile and liver function test were minor outcome measures. **Results**. Pioglitazone significantly improved major outcome measures compared with placebo. The decrease from baseline of total cholesterol level was more in pioglitazone- than in placebo-treated groups. In 84% (32 out of 38) of the sildenafil poor-responders, at least one of the associated risk factors of ED was found. There was undiagnosed hypercholesterolemia in 34% of the subjects. Serum levels of T, DHEAS, glucose and other parameters remained unchanged in both groups. The intervention was well tolerated. **Conclusions**. Pioglitazone increased sildenafil response to improve ED of men with prior sildenafil failure and seems to be safe based on the present preliminary study. This improvement is likely regardless of fasting glucose and sex hormones levels.

INTRODUCTION

Erectile dysfunction (ED) is a prevalent and chronic disorder in men over 40 years old (1, 2) and its incidence has increased because of limited physical activity and high calorie intake associated with modern lifestyle (3). Common in risk factors, ED is often observed in patients with cardiovascular co-morbidities and precedes coronary artery disease (4, 5).

In penile erection, nitric oxide (NO)-activated soluble guanylyl cyclase synthesizes cyclic guanosine monophosphate (cGMP) which results in relaxation of arterial and trabecular smooth muscles. Sildenafil augments these smooth muscle relaxations by inhibition of phosphodiesterase-5 (PDE-5), the enzyme that breakdowns cGMP.

Even though sildenafil has been extensively prescribed as the first line drug in treatment of ED for years, there are reports of sildenafil discontinuation mainly due to the lack of effectiveness in more than 70% of men who stop sildenafil usage (6). Even after optimized instruction for sildenafil usage (7) or switching to more potent drugs of PDE-5 inhibitors family, with either on-demand or daily usage, the success rate of intercourse attempts could not reach more than 50% (8, 9). Apart from oral treatments for ED, alternative choices such as intracavernousal injectable drugs, penile protheses and vacuum devices have disadvantages including cost, invasiveness and rather artificial sexual relationship.

Corresponding Author: Dr. M. Mahmoudian, Pharmacology Department, Iran University of Medical Sciences, Hemmat Highway, P.O. Box: 14155-6183, Tehran, Iran. E-mail: masmah99@iums.ac.ir

Conclusively, for a considerable percentage of men with ED who are seeking new treatment modalities, planning new therapeutic measures is necessary.

Because of ambiguities and controversies on common findings in sildenafil non-responders, there is no definite clinical criteria to predict sildenafil failure (10, 11), although men with diabetic and neurogenic ED have a higher dissatisfaction rate (6). Ineffectiveness of sildenafil in ED has been shown by a few studies from genetical, physiological, histopathological and hemodynamic aspects. It is suggested that endothelial nitric oxide synthase (NOS 3) and angiotensin converting enzyme (ACE) genotypes influence the erectile response to sildenafil (12). Severe vascular lesions and atrophy of smooth muscle cells (SMCs) were observed in sildenafil nonresponders (10). It has been showed that response to sildenafil could not be predicted by endothelial and autonomic systemic function tests, but in diabetic men it appears to be related to the initial degree of ED (13). Doppler ultrasonography studies of penile vessels showed poor rigidity response to intracavernous injection of vasodilators, penile arterial insufficiency and veno-occlusive dysfunction (14, 15). Based on some associated findings in this complex and multi-factorial disorder, drugs that maintain the structure and function of penile vasculature by preventing endothelial and SMCs dysfunction and damage, may improve response to sildenafil.

In optimizing response to sildenafil, the candidate drug must have a unique safety profile: 1- high safety especially in geriatrics as the leading age group of ED; 2- few interactions with drugs used for co-morbid diseases and with sildenafil especially for the risk of acute hemodynamic-induced events. Preliminary studies have shown improved response to sildenafil by quinapril and atorvastatin (16, 17). Peroxisome prolifrator-activated receptor γ ligands (PPARγ), including pioglitazone, demonstrated beneficial effects on ED predisposing factors such as endothelial dysfunction, oxidative stress, metabolic disorders, atherosclerosis and inflammation (18, 19). Promisingly, pioglitazone has already been shown to prevent veno-occlusive ED in diabetic rats by a mechanism independent of glycaemic control (20). Therefore, the present study was conducted to examine whether premedication with pioglitazone is devoid of any adverse drug events and can improve responsiveness to sildenafil in men with ED.

METHODS

Subjects

Study population were 38 men (age: 35-70) with ED ranging from moderate to severe as defined by International Index of Erectile Function (IIEF) questionnaire (21, 22). They had to have a stable sexual relationship and inadequate response to sildenafil citrate. Poor response to sildenafil was defined as: having the experience of at least four unsuccessful intercourse attempts in nonsuccessive occasions after being oriented to use the highest tolerable and therapeutic dose (≤100 mg) with respect to timing relative to meals, use of concomitant medications and adequate sexual stimulation. Subjects were excluded from participation in respect to any of the followings: 1- existing disease: neuropathic (diabetic/nondiabetic), endocrinopathic and psychogenic ED, anatomical penile abnormality, heart failure (class II - IV), serum alanine aminotransferase (ALT) > two fold the upper limit of normal values, unstable cardiovascular hemodynamic (e.g. coronary syndrome, hypotension); 2- medications: substance abuse, nitrate and steroid regimens; 3- assessment tool (IIEF questionnaire) limitations: low sexual desire and EF score <5, sexual dysfunction in partner, lack of a stable heterosexual relationship (21, 22). The study was conducted in accordance and conformation with the Declaration of Helsinki. The protocol was reviewed and approved by the ethical committee board of Razi Institute for Drug Research, Iran University of Medical Sciences.

Study design

This study was designed as a prospective, randomized, placebo-controlled, double-blinded trial. Subjects enrolled voluntarily following an announcement in the Iran University of Medical Sciences. The same physician carried out all the study interviews and examinations. Signed written informed consent was obtained from each subject after full oral and written explanation of the purpose, nature, duration and risk of all procedures

for the patients. All subjects were clinically assessed based on a medical/sexual history and physical examination including measurements of body mass index (BMI) and waist to hip ratio (W/H). Following a 4 weeks run-in period for sildenafil trial, baseline self-reported questionnaires and blood tests were obtained from all patients. Eligible patients were assigned to receive either pioglitazone 30 mg once daily or matching placebo according to a randomization table for nine weeks. All patients were requested to have intercourse at least once weekly in the last month of pioglitazone treatment along with on-demand use of sildenafil. The laboratory staffs involved in the intervention were not aware of the group assignment. Medical visits were scheduled at 4-weeks intervals for 12 weeks to check possible adverse events, lifestyle changes and patients' compliance. For the second time, at the end of intervention period, self-completed questionnaires and blood tests were obtained from the patients. BMI > 28.7 kg/m², diabetes, hypercholesterolemia, hypertension and smoking were regarded as associated risk factors of ED (2-5, 27).

Erectile dysfunction assessment

In this study, a specific version of IIEF questionnaire, i.e. erectile function (EF) domain, was used as the assessment instrument for measurement of erectile function and interventional efficacy (21). As the gold standard instrument, the IIEF is an extensively used and highly validated instrument for the evaluation of sexual function in men especially in clinical trials(21-24). EF domain is a 6 items version of IIEF questionnaire that grades erectile function by responses to six specific questions of IIEF questionnaire; Question 1-5 are related to EF segment of IIEF and the last question concerns erectile confidence, i.e., question 15 IIEF (25, 26). The scores of EF domain of IIEF were clinically interpreted as: no ED >26, mild ED = 22 to 25, mild-to-moderate ED=17 to 21, moderate ED = 11 to16 and severe ED <10 (25).

Besides the use of EF domain of IIEF for definition of functional severity of ED for inclusion (IIEF EF domain <17), it is also used for measurement of the impact size of pioglitazone on sildenafil efficacy in erectile function by comparing the secondary IIEF EF domain scores with the baseline scores (22). In addition, as qualitative measures, two questions of global assessment questions(GAQs) was asked from the patients at study end point (22):1- ''Has the treatment you have been taking during this study improved your erections?" (GAQ Q1) and ''If yes, 2- Has the treatment improved your ability to engage in sexual activity?"(GAQ Q2).

Laboratory assessment

Laboratory blood tests were done for all subjects at the beginning and at the end of study. Serum samples were obtained after an overnight fasting and immediately processed and kept frozen at -20°C until the assay was carried out. Serum level of glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein (LDL), triglycerides (TG), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Serum glucose was measured by glucose-oxidase method. Serum lipid levels, ALT and AST were assayed directly by standard enzymatic methods. Total testosterone (T) and Dehydroepiandrosterone sulfate (DHEAs) were measured with available radioimmunologic kits from Biosourse, Belgium (reference limit: 1.34-6.25 ng/ml) and from Immunotech, France (reference limit: 133-441 mcg/dl). Supported by external quality control, lab analysis was done in Comprehensive Hemophilia Care Center (CHCC) of Iran, a member of UK National External Quality Assessment Service (UKNEQAS).

Statistical analysis

Erectile function scores was regarded as the major outcome measure of present study and values of laboratory biomarkers were considered to be the minor outcome measures. Continuous variable data were analyzed by two-tailed Student's unpaired t-test to assess inter-group differences and paired t-test to assess the longitudinal differences in each group. For discrete variables, chi-square test was used to assess differences in proportions of incidence between the two groups. Correlations between changes in variables were assessed with Pearson's correlation coefficient. Data were expressed as mean ± SEM. In all tests, $p < 0.05$ (2-tailed) was considered to be statistically significant.

RESULTS

Of 45 men who were re-challenged for sildenafil, 40 men (88%) were true poor-/non-responders and entered the study. Thirty eight men (95 %) completed the study. Two subjects dropped out, one in placebo group due to urgent coronary bypass surgery and one in drug group for a job offer in another city. The prevalence of associated risk factors was similar in both groups. 84% of patients (32 out of 38) had at least one risk factor and 47% of patients (18 out of 38) had two risk factors. Regarding a threshold of 195 mg/dl for total cholesterol, one third of all participants (13 out of 38) were unaware of their hypercholestrolemia until their first blood test in this study. Baseline characteristics and measured data of subjects are shown in Table 1 & 2.

There were no statistically significant differences between the drug and control groups with respect to baseline characteristics, EF domain scores and laboratory parameters except for TG level, which were higher in placebo group ($p< 0.02$). The latter was probably influenced by undiagnosed familial hypertriglyceridemia (TG = 599 mg/dl) in one patient.

Erectile function profile

Erectile function score improved in the pioglitazone group, but remained stable in the placebo group. The mean EF domain of IIEF score was significantly increased from 13.32 ± 0.60 to 17.63 ± 1.05 in pioglitazaone group compared to the placebo group in which the EF score changed from 14.11 ± 0.56 to 14.32 ± 0.73,($p < 0.02$), Figure-1. Consequently, at the end point of intervention, the mean changes of IIEF EF domain score (Δ EF) from baseline was significantly higher in the pioglitazone group compared to the mean changes in placebo group (4.32 ± 0.7 vs. 0.21 ± 0.44, $p< 0.001$).

In drug group, compared with placebo, the mean response to every six questions of EF domain improved and this improvement was significant ($p <0.03$) with respect to erection frequency (IIEF Q1), erection maintenance frequency (IIEF Q4) and erection maintenance ability (IIEF Q5). According to clinical classification of IIEF EF domain scores, stage of ED in the pioglitazone group raised from moderate ED range level to the mild-to-moderate range level. At 9 weeks, the proportion of positive responses to the GAQs was significantly greater in patients receiving pioglitazone (11/19) than in patients receiving placebo (2/19) Table- 3.

In pioglitazone group, the difference between the mean change of EF scores in diabetics and nondiabetics (3.16 ± 1.27 vs 4.84 ± 0.84, respectively) was not significant. Also, in diabetics of drug and control groups, the mean changes of EF scores (3.16 ± 1.27 vs $- 0.25 \pm 0.25$, respectively) were not significantly different.

Table 1. Baseline characteristics and prevalence of erectile dysfunction risk factors in study subjects.

	Total	Placebo	Pioglitazone
n	38	19	19
Age (yr)	47 ± 1.45	45 ± 1.67	49 ± 2.34
BMI > 28.7 (Kg/m²)	16 (42%)	8 (42%)	8 (42%)
Diabetes	10 (26%)	4 (21%)	6 (32%)
Hypertension	8 (21%)	4 (21%)	4 (21%)
Hypercholestrolemia	13 (34%)	6 (32%)	7 (37%)
Smoking	6 (16%)	4 (21%)	2 (11%)

Table 2. Measured variables and IIEF EF domain scores of study subjects at baseline and endpoint.

	Placebo (n=19)		Pioglitazone (n=19)			
	Week 0	Week 9	Week 0	Week 9	p1	p2
BMI, Kg/m^2	28.79 ± 1.32	28.70 ± 1.33	28.60 ± 1.22	28.68 ± 1.20	0.916	0.990
W/H	0.97 ± 0.01	0.971 ± 0.01	0.96 ± 0.01	0.95 ± 0.01	0.403	0.253
SBP, mmHg	127.37 ± 3.573	126.58 ± 3.86	129.71 ± 3.84	127.94 ± 3.61	0.632	0.692
DBP, mmHg	81.05 ± 2.28	80 ± 2.16	83.82 ± 2.36	82.35 ± 2.33	0.736	0.805
FBS, mg/dL	110.90 ± 7.53	104.58 ± 3.98	127.26 ± 13.55	115.32 ± 12.02	0.298	0.402
ΔFBS, mg/dL	-6.32 ± 5.905		-11.95 ± 6.90		0.539	
Cholestrol, mg/dL	197.34 ± 8.94	200.90 ± 9.52	198 ± 8.38	183.47 ± 7.80	0.957	0.165
ΔCholestrol, mg/dL	3.56 ± 6.35		-14.53 ± 4.03		0.022*	
LDL mg/dL	102.13 ± 5.89	99.70 ± 4.70	106.63 ± 5.31	97.91 ± 5.34	0.574	0.803
ΔLDL, mg/dL	-2.43 ± 4.49		-8.721 ± 2.66		0.236	
HDL, mg/dL	34.67 ± 1.99	35.33 ± 1.98	37.98 ± 2.36	38.86 ± 2.27	0.290	0.248
ΔHDL mg/dL	0.65 ± 1.34		0.88 ± 0.98		0.893	
Triglycerides mg/dL	215.21 ± 30.19	234.11±38.85	130.368± 14.702	128.789±18.28	0.016*	0.019*
Δtriglycerides mg/dL	18.90 ± 22.16		-1.58 ± 10.88		0.412	
AST mg/dL	24.63 ± 2.11	24.12 ± 1.28	21.37 ± 1.56	21.95 ± 1.24	0.221	0.232
ΔAST mg/dL	-0.53 ± 1.40		0.58 ± 1.248		0.559	
ALT, mg/dL	33.68 ± 4.24	36.32 ± 3.16	26.37 ± 3.58	28.79 ± 2.31	0.195	0.062
ΔALT, mg/dL	2.63 ± 2.74		2.42 ± 2.44		0.954	
Testosterone ng/mL	3.66 ± 0.33	3.55 ± 0.36	4.38 ± 0.23	4.257 ± 0.25	0.081	0.117
ΔTestosterone, ng/ml	-0.107 ± 0.203		-0.118 ± 0.226		0.973	
DHEAS, mcg/dL	162.71 ± 15.08	156.21±16.44	124.40 ± 13.00	119.12 ± 11.16	0.062	0.070
ΔDHEAS, mcg/dL	-6.499 ± 8.363		-5.284 ± 6.895		0.911	
IIEF EF Domain	14.11 ± 0.56	14.32 ± 0.73	13.32 ± 0.60	17.63 ± 1.05	0.340	0.014*
ΔIIEF EF Domain	0.21 ± 0.44		4.32 ± 0.71		<0.001*	

Data are means ± SEM; Δ, p_1,values for baseline comparison between placebo & pioglitazone; p2, values for end point comparison between placebo & pioglitazone; * Significant different from placebo.

Laboratory parameters

At the endpoint, a significant decrease in mean change of total cholesterol concentration was observed in pioglitazone group compared to placebo group (-14.53 ± 4.03 vs. 3.56 ± 6.35, P = 0.022). Compared to the baseline, LDL cholesterol significantly decreased in drug group (106.63 ± 5.31 vs. 97.91 ± 5.34. $p < 0.05$) but compared to placebo this reduction became nonsignificant. At

study end, TG levels in placebo group remained significantly higher than those in drug group but the mean changes in TG concentration in drug group vs. placebo group were nonsignificant. There were no correlation between the changes of total cholesterol levels, fasting blood glucose or other measured parameters and improvement of EF scores while an inverse correlation was found between the decreases of total cholesterol and age ($r = - 0.33$, $p < 0.05$). Pioglitazone improved erectile function

Table 3. Patients % reporting improved erection (Q1) & sexual activity (Q2).

Response to questions	Placebo	pioglitazone	p value
Positive to GAQ Q1	11%	58%	0.024*
Positive to GAQ Q 2	11%	58%	0.024*

irrespective of glucose level. Pioglitazone did not influence serum level of T and DHEAS in either group. Other laboratory parameters as well as BMI and W/H in drug group did not change significantly compared to those in control group.

Mild and transient adverse events were detected in only two patients receiving pioglitazone, ie, symmetrical hand edema and urinary frequency. Treatment with pioglitazone was generally well tolerated and with respect to co-administration of pioglitazone and sildenafil, no clinical drug interaction was observed. Treatment with pioglitazone improved urinary flow of one patient with slow-flowing urine.

DISCUSSION

Pioglitazone treatment significantly improved sildenafil responsiveness in men with erectile dysfunction who initially did not gain adequate response from sildenafil therapy alone. Since the duration of the study was not thoroughly sufficient for pioglitazone to exert its anti-diabetic action (20) and fasting blood glucose was not significantly influenced by the intervention, the ED improvement is likely irrespective of serum glucose level. This intervention, performed in the present preliminary study, appears to be safe and had no unfavorable effects on the measured markers.

To our knowledge the current study is the only clinical investigation that evaluated the effects of a PPARγ agonist in ED. Risk factors for cardiovascular disease could affect every integrated part of systemic vessels especially penile vasculature. Since clinically significant penile vascular disease precedes overt atherosclerosis in other arteries, e.g. coronary artery (28), ED itself might be potentially used as a pre-screening tool for evaluation of cardiovascular disease and its risk factors (5). As seen in many subjects participated in the present study, hyperlipidemia and especially hypercholesterolemia, were diagnosed for the first time, during the initial work up for ED and there was a co-incidence of ED with co-morbid diseases among sildenafil nonresponders. In drug and control groups, high incidence of risk factors including diabetes, hypertension, dyslipidemia, smoking along with the upper borders of the normal ranges in mean levels of serum glucose, cholesterol, LDL, TG, W/H and BMI were observed before the intervention. These findings are in consistence with those of other reports (27, 29).

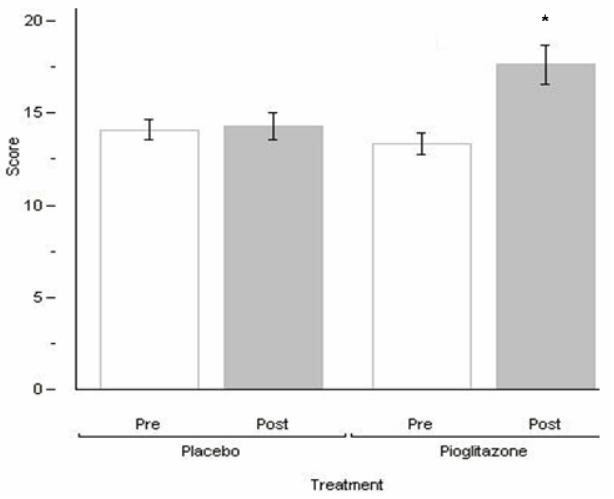

Figure 1. Effects of placebo and pioglitazone on the EF domain of IIEF at baseline and at 9 weeks. *$p < 0.05$ for endpoint comparison with placebo

Some evidence could help to figure out potential mechanisms for improvement of ED in this study. Endothelium-dependent vasodilation is impaired by high cholesterol (30) and cholesterol-lowering therapy could ameliorate endothelium-dependent relaxation (31). In the present study,

improvement of ED coincided with lowering of total serum cholesterol by pioglitazone as shown by other cholesterol lowering therapies such as statins (32). Although a significant correlation was not detected between these two parameters, more extensive studies are needed to clarify if there is a cause and effect relation.

It has been suggested that baseline EF score and apolipoprotein B determine responsiveness to sildenafil (33). Although apolipoproteins were not measured in this study but pioglitazone does exert apolipoprotein B-lowering effect (34). Thus, ED improvement, at least in part, could be attributed to this effect (34).

Niric-oxide (NO) production and release is augmented by thiazolidinediones (TZDs) at cellular level (35, 36). Also, pioglitazone increases NO bioavailability and improves endothelium dependent vasodilation through increasing adiponectin and insulin sensitivity or decreasing C-reactive protein (CRP), free fatty acids (FFA) and asymmetric dimethylarginine (ADMA) (19, 34, 37).

Inhibition of Rho/Rho-kinase signaling pathway by pioglitazone (38) might be one of the mechanisms for ED amelioration in our patients. This pathway was up-regulated in the corporal vasculature of diabetic rats with ED and its inhibition might enhance suppressed penile eNOS expression and cGMP levels, to restore erectile function (39).

In the only animal study that investigated the effects of pioglitazone in veno-oclusive model of diabetic erectile dysfunction, pioglitazone decreased apoptotic index, relative collagen content (collagen/SMC area) and collagen III/I ratios in corpous cavernosa (CC) along with a reduction in systemic oxidative stress in 9 weeks. In long term piogitazone even prevented corporal veno-occlusive dysfunction and improved papaverin response (20). However, this study is incomparable with ours in study groups and dose equivalency.

In the current study, pioglitazone was preferred to rosiglitazone, with a conservative dose of 30mg/day to optimize the balance between probable clinical responses and side effects. Apart from high safety data of pioglitazone (40, 41), there is a potential for interaction of rosiglitazone with sildenafil to augment the systemic effects of NO, as rosiglitazone has shown direct coronary vasodilatory effects while pioglitazone has not (42). Furthermore, with a local lower cost, pioglitazone has shown more favorable effects on lipid profile compared to unfavorable properties of rosigitazone (43, 44). Meta-analyses suggested an increased cardiovascular risk associated with rosiglitazone therapy (44).

To our knowledge, the current study for the first time showed the impact of pioglitazone on serum level of T and DHEAS in men. In the only one previous study, rosiglitazone decreased the production rate of T in one week (45) but the latter and present study are different in medication, sample size, duration, characteristics of subjects and measurement methods. There is no report of impotence and decreased libido following pioglitazone therapy (40, 41). In the current study after the intervention, the mean levels of total T and DHEAS did not change significantly.

Small sample size might be regarded as a limitation for present study but to gain stepwise experiences in the lack of background clinical study of pioglitazone in ED, our sample size seems to be adequately large to fulfill the main initial objectives of the study although this sample size is not sufficient to entirely address the safety of the intervention.

The mean change of EF scores was almost clinically significant, based on IIEF scores interpretation (22), and also consistently supported by results of GAQs. This increase in mean score was not much more than 4 in pioglitazone group. The relative short period of the intervention might be responsible for this result and also for the insignificant impact of the intervention on the most of serum lipids.

In post follow-up visits, nearly 40% of drug group subjects decided to continue using pioglitazone to maintain improved erectile function and attain glucose control. Many of vasculoprotective effects of pioglitazone appear gradually (20) and, thus, in long-term treatment the EF scores could increase more than what we observed. In such condition, pioglitazone may also influence high glucose levels, if any, and the results must be interpreted accordingly. On the contrary to many similar studies, the negligible improvement of ED in our placebo group shows an unaccountable positive psychogenic feedback in the patients thus the ED improvement in drug group may be devoid of considerable psychogenic origin and almost

could be attributed to the pharmacological properties of pioglitazone.

Urinary symptoms associated with pioglitazone treatment could be attributed to water retention in renal collecting ducts (34). Finally, by considering the present study as a preliminary evaluation of the benefits/risks of pioglitanzone treatment in ED patients, the results of this study could be implemented with optimization for a large trial.

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REFERENCES

[1]. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol, 151:54-61, 1994.

[2]. Kubin M, Wagner G, Fugl-Meyer AR. Epidemiology of erectile dysfunction. Int J Impot Res, 15:63-71, 2003.

[3]. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. Ann Intern Med, 139:161-168, 2003.

[4]. Grover SA, Lowensteyn I, Kaouache M, Marchand S, Coupal L, DeCarolis E, Zoccoli J, Defoy I. The prevalence of erectile dysfunction in the primary care setting: importance of risk factors for diabetes and vascular disease. Arch Intern Med, 166:213-219, 2006.

[5]. Montorsi F, Briganti A, Salonia A, Rigatti P, Margonato A, Macchi A, Galli S, Ravagnani PM, Montorsi P. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol, 44:360-364; discussion 364-365, 2003.

[6]. Souverein PC, Egberts AC, Meuleman EJ, Urquhart J, Leufkens HG. Incidence and determinants of sildenafil (dis)continuation: the Dutch cohort of sildenafil users. Int J Impot Res, 14:259-265, 2002.

[7]. Atiemo HO, Szostak MJ, Sklar GN. Salvage of sildenafil failures referred from primary care physicians. J Urol, 170:2356-2358, 2003.

[8]. Hatzimouratidis K, Moysidis K, Bekos A, Tsimtsiou Z, Ioannidis E, Hatzichristou D. Treatment strategy for "non-responders" to tadalafil and vardenafil: a real-life study. Eur Urol, 50:126-132; discussion 132-123, 2006.

[9]. Carson CC, Hatzichristou DG, Carrier S, Lording D, Lyngdorf P, Aliotta P, Auerbach S, Murdock M, Wilkins HJ, McBride TA, Colopy MW. Erectile response with vardenafil in sildenafil nonresponders: a multicentre, double-blind, 12-week, flexible-dose, placebo-controlled erectile dysfunction clinical trial. BJU Int, 94:1301-1309, 2004.

[10]. Wespes E, Rammal A, Garbar C. Sildenafil non-responders: haemodynamic and morphometric studies. Eur Urol, 48:136-139; discussion 139, 2005.

[11]. Jarow JP, Burnett AL, Geringer AM. Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment. J Urol, 162:722-725, 1999.

[12]. Eisenhardt A, Sperling H, Hauck E, Porst H, Stief C, Rubben H, Muller N, Siffert W. ACE gene I/D and NOS3 G894T polymorphisms and response to sildenafil in men with erectile dysfunction. Urology, 62:152-157, 2003.

[13]. Pegge NC, Twomey AM, Vaughton K, Gravenor MB, Ramsey MW, Price DE. The role of endothelial dysfunction in the pathophysiology of erectile dysfunction in diabetes and in determining response to treatment. Diabet Med, 23:873-878, 2006.

[14]. Brisson TE, Broderick GA, Thiel DD, Heckman MG, Pinkstaff DM. Vardenafil rescue rates of sildenafil nonresponders: objective assessment of 327 patients with erectile dysfunction. Urology, 68:397-401, 2006.

[15]. Huang ST, Hsieh ML. Different hemodynamic responses by color Doppler ultrasonography studies between sildenafil non-responders and responders. Asian J Androl, 9:129-133, 2007.

[16]. Bank AJ, Kelly AS, Kaiser DR, Crawford WW, Waxman B, Schow DA, Billups KL. The effects of quinapril and atorvastatin on the responsiveness to sildenafil in men with erectile dysfunction. Vasc Med, 11:251-257, 2006.

[17]. Herrmann HC, Levine LA, Macaluso J, Jr., Walsh

M, Bradbury D, Schwartz S, Mohler ER, 3rd, Kimmel SE. Can atorvastatin improve the response to sildenafil in men with erectile dysfunction not initially responsive to sildenafil? Hypothesis and pilot trial results. J Sex Med, 3:303-308, 2006.

[18]. Giannini S, Serio M, Galli A. Pleiotropic effects of thiazolidinediones: taking a look beyond antidiabetic activity. J Endocrinol Invest, 27:982-991, 2004.

[19]. Martens FM, Visseren FL, de Koning EJ, Rabelink TJ. Short-term pioglitazone treatment improves vascular function irrespective of metabolic changes in patients with type 2 diabetes. J Cardiovasc Pharmacol, 46:773-778, 2005.

[20]. Kovanecz I, Ferrini MG, Vernet D, Nolazco G, Rajfer J, Gonzalez-Cadavid NF. Pioglitazone prevents corporal veno-occlusive dysfunction in a rat model of type 2 diabetes mellitus. BJU Int, 98:116-124, 2006.

[21]. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology, 49:822-830, 1997.

[22]. Rosen RC, Althof SE, Giuliano F. Research instruments for the diagnosis and treatment of patients with erectile dysfunction. Urology, 68:6-16, 2006.

[23]. Dula E, Keating W, Siami PF, Edmonds A, O'Neil J, Buttler S. Efficacy and safety of fixed-dose and dose-optimization regimens of sublingual apomorphine versus placebo in men with erectile dysfunction. The Apomorphine Study Group. Urology, 56:130-135, 2000.

[24]. Rosen RC, Cappelleri JC, Gendrano N, 3rd. The International Index of Erectile Function (IIEF): a state-of-the-science review. Int J Impot Res, 14:226-244, 2002.

[25]. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. Urology, 54:346-351, 1999.

[26]. Cappelleri JC, Siegel RL, Osterloh IH, Rosen RC. Relationship between patient self-assessment of erectile function and the erectile function domain of the international index of erectile function. Urology, 56:477-481, 2000.

[27]. Ponholzer A, Temml C, Mock K, Marszalek M, Obermayr R, Madersbacher S. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. Eur Urol, 47:80-85; discussion 85-86, 2005.

[28]. Kaiser DR, Billups K, Mason C, Wetterling R, Lundberg JL, Bank AJ. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. J Am Coll Cardiol, 43:179-84, 2004.

[29]. Wei M, Macera CA, Davis DR, Hornung CA, Nankin HR, Blair SN. Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. Am J Epidemiol, 140:930-937, 1994.

[30]. Azadzoi KM, Saenz de Tejada I. Hypercholesterolemia impairs endothelium-dependent relaxation of rabbit corpus cavernosum smooth muscle. J Urol, 146:238-240, 1991.

[31]. Leung WH, Lau CP, Wong CK. Beneficial effect of cholesterol-lowering therapy on coronary endothelium-dependent relaxation in hypercholesterolaemic patients. Lancet, 341:1496-1500, 1993.

[32]. Saltzman EA, Guay AT, Jacobson J. Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. J Urol, 172:255-258, 2004.

[33]. Solomon H, Wierzbicki AS, Lumb PJ, Lambert-Hammill M, Jackson G. Cardiovascular risk factors determine erectile and arterial function response to sildenafil. Am J Hypertens, 19:915-919, 2006.

[34]. Kendall DM, Rubin CJ, Mohideen P, Ledeine JM, Belder R, Gross J, Norwood P, O'Mahony M, Sall K, Sloan G, Roberts A, Fiedorek FT, DeFronzo RA. Improvement of glycemic control, triglycerides, and HDL cholesterol levels with muraglitazar, a dual (alpha/gamma) peroxisome proliferator-activated receptor activator, in patients with type 2 diabetes inadequately controlled with metformin monotherapy: A double-blind, randomized, pioglitazone-comparative study. Diabetes Care, 29:1016-1023, 2006.

[35]. Polikandriotis JA, Mazzella LJ, Rupnow HL, Hart CM. Peroxisome proliferator-activated receptor gamma ligands stimulate endothelial nitric oxide production through distinct peroxisome proliferator-activated receptor gamma-dependent mechanisms. Arterioscler Thromb Vasc Biol, 25:1810-1816, 2005.

[36]. Cho DH, Choi YJ, Jo SA, Jo I. Nitric oxide production and regulation of endothelial nitric-oxide synthase phosphorylation by prolonged treatment with troglitazone: evidence for involvement of peroxisome proliferator-activated receptor (PPAR) gamma-dependent and PPARgamma-independent signaling pathways. J Biol Chem, 279:2499-2506, 2004.

[37]. Wakino S, Hayashi K, Tatematsu S, Hasegawa K, Takamatsu I, Kanda T, Homma K, Yoshioka K, Sugano N, Saruta T. Pioglitazone lowers systemic asymmetric dimethylarginine by inducing dimethylarginine dimethylamino-hydrolase in rats. Hypertens Res, 28:255-262, 2005.

[38]. Wakino S, Hayashi K, Kanda T, Tatematsu S, Homma K, Yoshioka K, Takamatsu I, Saruta T. Peroxisome proliferator-activated receptor gamma ligands inhibit Rho/Rho kinase pathway by inducing protein tyrosine phosphatase SHP-2. Circ Res, 95:e45-55, 2004.

[39]. Bivalacqua TJ, Champion HC, Usta MF, Cellek S, Chitaley K, Webb RC, Lewis RL, Mills TM, Hellstrom WJ, Kadowitz PJ. RhoA/Rho-kinase suppresses endothelial nitric oxide synthase in the penis: a mechanism for diabetes-associated erectile dysfunction. Proc Natl Acad Sci U S A, 101:9121-9126, 2004.

[40]. Kawamori R, Kadowaki T, Onji M, Seino Y, Akanuma Y. Hepatic safety profile and glycemic control of pioglitazone in more than 20,000 patients with type 2 diabetes mellitus: postmarketing surveillance study in Japan. Diabetes Res Clin Pract, 76:229-235, 2007.

[41]. Belcher G, Lambert C, Edwards G, Urquhart R, Matthews DR. Safety and tolerability of pioglitazone, metformin, and gliclazide in the treatment of type 2 diabetes. Diabetes Res Clin Pract, 70:53-62, 2005.

[42]. Uchida K, Ogino K, Shimoyama M, Hisatome I, Shigemasa C. Acute hemodynamic effects of insulin-sensitizing agents in isolated perfused rat hearts. Eur J Pharmacol, 400:113-119, 2000.

[43]. Derosa G, Cicero AF, D'Angelo A, Gaddi A, Ciccarelli L, Piccinni MN, Salvadeo SA, Pricolo F, Ferrari I, Gravina A, Ragonesi PD. Effects of 1 year of treatment with pioglitazone or rosiglitazone added to glimepiride on lipoprotein (a) and homocysteine concentrations in patients with type 2 diabetes mellitus and metabolic syndrome: a multicenter, randomized, double-blind, controlled clinical trial. Clin Ther, 28:679-688, 2006.

[44]. Rottlaender D, Michels G, Erdmann E, Hoppe UC. Therapy with glitazones--a risk for cardiovascular disease? Dtsch Med Wochenschr,132:2629-2632, 2007.

[45]. Vierhapper H, Nowotny P, Waldhausl W. Reduced production rates of testosterone and dihydrotestosterone in healthy men treated with rosiglitazone. Metabolism, 52:230-232, 2003.