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PDE5A Polymorphisms Influence on Sildenafil Treatment Success

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ABSTRACT

Introduction: Diabetes and cardiovascular disease are risk factors for erectile dysfunction (ED). Selective inhibitors of the type 5 phosphodiesterase are the first option for treating ED. However, it is unknown why there are patients with low response to this treatment. Polymorphisms in the *PDE5A* gene may influence the response to PDE5 inhibitors treatment.

Aim: The aim of this study is to analyze the relationship between *PDE5A* polymorphisms, diabetes, and the efficacy of sildenafil treatment.

Methods: A Spanish prospective cohort of 170 Caucasian male patients diagnosed with ED and ischemic heart disease treated with angioplasty was studied.

Main outcome measures: ED was evaluated according to the 5-item version of the International Index for Erectile Function before and after treatment with sildenafil 50 mg. The gene sequence of the *PDE5A* gene was analyzed for the presence of rs12646525 and rs3806808 polymorphisms. Glucose and glycosylated hemoglobin levels were measured in blood serum samples. The relationship between treatment response, genotype, and glycemic status was analyzed.

Results: Patients with G-allele of rs3806808 polymorphism showed a worse response to the treatment compared to TT-homozygote patients. Nondiabetic G-allele carriers showed a worse treatment response than TT-homozygotes patients. These differences were not seen in diabetic patients. There were no significant differences in treatment response according to the rs12646525 polymorphism in total population or according to the glycemic status. Logistic regression analysis showed that nondiabetic carriers of the major allele of both the rs12646525 and rs3806808 polymorphism had a significantly higher likelihood to respond to the treatment than diabetic patients carriers of the minor allele ($P < .05$).

Conclusion: The response to sildenafil treatment depends on polymorphisms in the *PDE5A* gene and the glycemic status of the patients.

Key Words: PDE5 polymorphism; Sildenafil; Erectile dysfunction; Diabetic

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to achieve and/or maintain a penile erection sufficient for sexual performance.[1]

Prevalence studies have identified age, obesity, diabetes, hypertension, and cardiovascular disease (CVD), among others, as risk factors for ED.[2–4]

There is a significant overlap of ED common risk factors with those of CVD. Besides, published studies suggest that ED could be the manifestation of generalized or focal arterial disease.[5–9] Indeed, in a cohort study of 420 patients from a cardiac rehabilitation program, 52.6% of patients presented ED with different

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Therefore, it would be interesting to further analyze the function of PDE5 in patients with and without this allele. Our study is coincident with the Lin et al study, which reported a lower frequency of the G-allele of rs3806808 gene in our group of patients.[13] However, in our case the presence of the G-allele was not associated with higher values of systolic blood pressure. In the cohort presented in this study, polymorphisms of rs3806808 of *PDE5A* gene in conjunction with glucose levels modulate the response to sildenafil 50 mg treatment based on the IIEF-5 test. When a distribution analysis was performed using obese and diabetic status with respect to response or nonresponse to treatment, we did not observe a statistically significant difference ($P > .05$). However, the distribution of being diabetic and having the less frequent allele of PDE5 polymorphism regarding DE severity and obesity (BMI > 30) showed significant differences ($P < .05$) in both cases (data not shown). This data reinforce the association between the less frequent allele and diabetic status in the response to sildenafil treatment. Moreover, our results indicate that the response to treatment does not depend only on the polymorphism, but also on the obesity and the severity of the ED of the patient, and therefore a more rational use of the treatment should be established.

Limitation

Although this study included a small cohort, these preliminary results highlight the need to study *PDE5A* polymorphisms in relation to ED in bigger cohorts to discern which patients would benefit from sildenafil treatment.

CONCLUSION

The response to sildenafil treatment depends on polymorphisms in the *PDE5A* gene and on the glycemic status of the patients.

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