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Myoinositol/folic acid combination for the treatment of erectile dysfunction in type 2 diabetes men: a double-blind, randomized, placebo-controlled study

R. AGOSTINI, F. ROSSI, R. PAJALICH*.

First Institute of Obstetrics and Gynecology, University La Sapienza – Rome (Italy)
*Ars Medica (S.P.A.) – Rome (Italy)

Abstract. – Erectile dysfunction is a common complication of diabetes. Diabetes can cause neuropathy or damage to nerves throughout your body, including the penis. Damaged nerves can't communicate properly. So even though you might be emotionally stimulated to have intercourse, nerve damage means that information isn't relayed to the penis, and it doesn't respond.

In addition, poor blood sugar control can inhibit nitric oxide production. Lack of nitric oxide can prevent the pressure of blood in the corpora cavernosa from rising enough to close off penile veins, allowing blood to flow out of the penis instead of remaining trapped for an erection. This prospective, randomized, double-blind, placebo-controlled study included 176 patients with type 2 diabetes. The daily 4 g dose of inositol plus 400 µg of folic acid or placebo was divided and given in three doses. The present study demonstrates that Myoinositol/folic acid combination, deserves consideration as therapeutic agent for preventing and treating erectile dysfunction in diabetic men, probably by virtue of both their chronic metabolic, acute ROS scavenging, and NO protective beneficial effects.

Key Words:

Myo-inositol, Folic acid, Erectile dysfunction, Type 2 diabetes.

Introduction

Erectile dysfunction (ED) is defined as the consistent inability to obtain or maintain an erection for satisfactory sexual intercourse. Basic science research on erectile physiology has been devoted to investigating the pathogenesis of ED and has led to the conclusion that ED is predominatly a disease of vascular origin. The incidence of ED dramatically increases in men with diabetes mellitus, hypercholesterolemia, and cardiovascular disease. Loss of the functional integrity of the endothelium and subsequent endothelial dysfunction plays an integral role in the occurrence of ED in this cohort of men.

Endothelial dysfunction may in part be related to uncoupling of the endothelial nitric oxide (NO) synthase enzyme, thus reducing the availability of NO. Folic acid may potentially reverse the uncoupling of NO synthase. Recently Title et al[1] showed that folic acid supplementation can improve endothelial dysfunction in type 2 diabetics independent of homocysteine-lowering.

It is also known that inositol can prevent and reverse endothelial dysfunction in diabetic rat and rabbit vessels, reduce elevated (reactive oxygen species) (ROS) in endothelial cells, potentiate nitrergic or vasculo-myogenic relaxations, and preserve NO signaling. These effects are related to its metabolic actions, direct superoxide scavenging, and enhancing and protecting NO signalling[2].

The aim of this study was to evaluate the effect of myo-inositol/folic acid combination on diabetics men with erectile dysfunction.

Materials and Methods

This prospective, randomized, double-blind, placebo-controlled study included 176 patients with type 2 diabetes (diabetes duration 4.4 ± 2.9 years), aged 50-70 years, with confirmed ED of > 6 months' duration, who were unable to achieve

Corresponding Author: Pravin J. Gupta, MD; e-mail: drpjg@yahoo.co.in

adequate erection and rigidity sufficient for vaginal penetration and completion of successful intercourse after spontaneous sexual stimulation.

All patients were either married or had stable heterosexual partners, and were men who were willing to improve their sexual function and agreed to cooperate in the protocol of all periodic follow-up assessments. Patients with severe cardiovascular diseases, cerebrovascular accident, uncontrolled hypertension, renal failure, hepatic insufficiency, endocrine abnormalities, psychiatric disorders, and evidence of dementia within 6 months or before the study onset were excluded.

Patients were excluded if they were currently or recently treated for their ED with a constriction ring, external vacuum devices, intracorporeal injection of vasoactive drugs, intraurethral application of vasoactive medications or had undergone prosthetic or reconstructive surgery on the penis before inclusion in the study.

Before entering the study, a detailed medical and sexual history was obtained from all participants. The studied patients underwent a complete physical examination, including the examination of the bulbocavernosus reflex and a penile haemodynamic study which included peak systolic velocity (PSV), end diastolic velocity (EDV) and resistance index (RI). All participants completed the questionnaire (Table I) introduced in 1999 by Rosen et al[3]. The cut-point was determined to be a score of 21. This score had a sensitivity of 98% and specificity of 88%, giving a likelihood ratio for a positive test of 8 and for a negative result of 0.02.

Finally, all participants were asked to keep a sexual activity diary during the study period.

The first 2 weeks of the study were a single-blind placebo run-in phase; at the end of this period, the patients were randomized to receive Myoinositol/folic acid combination or placebo therapy which lasted for 12 weeks. Identical powder of Myoinositol/folic acid combination (Inofolic – LO.LI Pharma Co., Rome, Italy) and placebo were used.

The daily 4 g dose of inositol plus 400 µg of folic acid or placebo was divided and given in three doses.

The medication was gave by the LO.LI Pharma Co., Italy, and randomization, registration and medication supply were controlled.

Physical examination and measurement of clinical variables, including duplex Doppler ultrasonography, were performed by one investigator. Patients were assessed 14 days before and at 0, 30, 60, and 90 days after treatment started.

Results

There were no significant differences between the two groups for type 2 diabetics in BMI (26.2 ± 3.5 versus 27.4 ± 3.0 kg/m^2, P = 0.40), choles-

Table I. IIEF-5 scoring system.

Over the past six months:	1	2	3	4	5
How do you rate your confidence that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
During sexual intercourse how difficult was it to maintain your erection to the completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always

The IIEF-5 score is the sum of questions 1 to 5. The lowest score is 5 and the highest score 25.

Table II. Comparison (Mean ± SEM) of the measured variables between the Myoinositol/folic acid group and placebo at the beginning and end of the study.

	Myoinositol/folic acid			Placebo		
	Pre	*Post*	*P value*	*Pre*	*Post*	*P value*
IIEF-5 score	12 ± 5	20 ± 3	< 0.05	14 ± 4	13 ± 4	NS
Sexual Function	8 ± 3	11 ± 1	< 0.05	9 ± 2	9 ± 1	NS
Sexual diary	1 ± 1	6 ± 1	< 0.05	1 ± 1	3 ± 1	NS
PSV	1143 ± 76	1732 ± 213	< 0.05	1231 ± 55	1352 ± 64	NS
EDV	644 ± 46	879 ± 78	< 0.05	752 ± 45	754 ± 56	NS
RI	0.5 ± 0.3	0.5 ± 04	NS	0.5 ± 0.2	0.4 ± 0.2	NS

terol (5.0 ± 0.9 versus 5.1 ± 0.9 mmol/L, P = 0.78), or HDL-cholesterol (1.0 ± 0.3 versus 1.1 ± 0.3 mmol/L, P = 0.44). The data of the study are reported in Table II.

The results were analysed statistically, with the mean ± SEM and Student's *t*-test (paired or unpaired as appropriate) used for statistical comparison. The chi-square test was used for continuous and discrete variables, with $P < 0.05$ considered to indicate significance.

Discussion

Endothelial dysfunction has been demonstrated in type 1 and type 2 diabetes. In the former, this alteration appears temporally linked to vascular disease and is more likely a consequence of the metabolic alterations that also explain the microangiopathy of this disease.

In type 2 diabetes, endothelial dysfunction is detectable very early in the course of the disease, even before overt hyperglycemia ensues, and may play a key role in the etiopathology of the vasculopathy associated with this disease.

Erectile dysfunction, sometimes called "impotence," is the repeated inability to get or keep an erection firm enough for sexual intercourse. The word "impotence" may also be used to describe other problems that interfere with sexual intercourse and reproduction, such as lack of sexual desire and problems with ejaculation or orgasm. Using the term erectile dysfunction makes it clear that those other problems are not involved. Damage to nerves, arteries, smooth muscles, and fibrous tissues, often as a result of disease, is the most common cause of ED. Diseases–such as diabetes, kidney disease, chronic alcoholism, multiple sclerosis, atherosclerosis, vascular disease, and neurologic disease–account for about 70 percent of ED cases. Erectile dysfunction (ED) affects up to 70% of men with diabetes. However, the pathophysiology of ED in diabetes remains uncertain with both neuronal and vascular factors cited[6]. *Myo*-inositol, the major nutritionally active form of inositol, is vital to many biological processes of the body, participating in a diverse range of activities. *Myo*-inositol is one of nine distinct isomers of inositol.

In the endocrinological clinical practice it is known that Inositol can help reverse nerve abnormalities related to diabetes[5]. Doshi SN et al. in 2001[7] demonstrated a significant improvement in endothelial function after 6 weeks of treatment with folic acid.

In conclusion, the present study demonstrates that Myoinositol/folic acid combination, deserves consideration as therapeutic agent for preventing and treating erectile dysfunction in diabetic men, probably by virtue of both their chronic metabolic, acute ROS scavenging, and NO protective beneficial effects[2,4].

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