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Research Article

Might Anti-Inflammatory Priming Enhance the Anti-Erectile Dysfunction Efficacy of PDE5 Inhibitors? An Exploratory Cohort Study

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Keywords

- Anti-inflammatory priming; Bromelain; Dietary supplements; Erectile dysfunction; Systemic inflammation

Abstract

Background: Evidences have long been accruing of a contributory role of low-grade systemic inflammation as co-determinant of erectile dysfunction. Inflammation and disruption of local microcirculation could also interfere with the full efficacy of PDE5 (phosphodiesterase type 5) inhibitors. The idea-generating pilot study herein explored is whether attenuating such pro-inflammatory contribution to the erectile dysfunctional milieu with the help of a dietary supplement could enhance the efficacy of PDE5 inhibitors.

Methods: 1.2.1. Study design: Prospective cohort pilot study (14 subjects with diagnosis of moderate erectile dysfunction) with end-of-study comparison of final treatment outcomes vs. a random sample of ED (erectile dysfunction) recent historic controls from the author's urology ward.

Cohort treatment: 1-month background anti-inflammatory priming with a dietary supplement of acknowledged anti-inflammatory and capillary protective properties (one 1-g tablet once daily) followed by 3 months of alternating every-other-day treatment with 25-mg sublingual sildenafil or the dietary supplement.

Assessments: comparison of the overall skewness of the cohort distribution of IIEF-5 (simplified International Index of Erectile Function) scores before and after the end of the treatment period, and purely exploratory comparison of the end-of-study EEIF-5 mean scores of the prospective cohort and the sample of historic controls.

Results: Strong left skewness of the IIEF-5 frequency distribution at the end of the study compared to the basal score distribution suggests controlling background inflammation might indeed be of value. EEIF-5 mean scores, prospective active cohort vs. ED historic controls: 20.4 vs. 14.0.

Conclusions: The exploratory comparison of end-of-treatment mean IIEF-5 scores in the active cohort vs. historic controls gives some preliminary support to the idea that modifying the pro-inflammatory erectile dysfunctional milieu with the anti-inflammatory dietary supplement might indeed have contributed to the overall efficacy of the anti-ED treatment and enhanced the 3-month efficacy of sublingual sildenafil. Further investigations are warranted to confirm these preliminary suggestions.

ABBREVIATIONS

cm/sec centimeter per second; CRP: C-Reactive Protein; ED: Erectile Dysfunction; hs-CRP: high-sensitivity C-Reactive Protein; hs-IL-6: high-sensitivity Interleukin-6; IIEF-5: simplified International Index of Erectile Function; ng/dL: nanograms per deciliter; NLR: Neutrophil to Lymphocyte count Ratio; PDE-5: Phosphodiesterase type 5; PPAR: Peroxisome Proliferator-Activated Receptor; PSA: Prostate Specific Antigen; PSV: Peak Systolic Velocity; TLR4: Toll-Like Receptor 4; TNF-α: Tumor Necrosis Factor-α

INTRODUCTION

Background

The inability to achieve and/or to maintain an erection adequate for satisfactory sexual activity has long been known to have endocrine, neurological, psychological, and iatrogenic causes; vasculogenic determinants are the leading contributors [1,2].

Many clues also hint at a role for inflammation and endothelial dysfunction in erectile dysfunction (ED). For instance,

the overlapping of the risk factors for vasculogenic ED and atherosclerosis is so impressive that ED and the inflammatory markers associated with ED might be considered early predictors of atherosclerosis and cardiovascular disease [2-4].

A large-scale Chinese 2019 study confirmed the ED predictive value even of a simple inflammatory marker as high-sensitivity C-reactive protein (hs-CRP) levels, with subjects in the highest hs-CRP level quartile showing a 50% increased likelihood of an ED diagnosis compared with individuals in the lowest quartile. Serum hs-CRP levels also correlated with the severity of the erectile dysfunction and efficiently discriminated severe ED [5].

A 2018 real-life study in 279 consecutive white Europeans with newly diagnosed ED also suggested that values higher than 3.0 of the neutrophil to lymphocyte count ratio (NLR), another simple marker of systemic inflammation, are a strong independent predictor of severe ED [6]. The same is true for the platelet-to-lymphocyte ratio, another low-cost marker of systemic inflammation and ED predictor [7].

The evidence, even after controlling for the contribution of cardiovascular risk factors, that ED severity is a good proxy for overall men's health also suggests an important role for systemic inflammation [8]. This is also the case for the increasing evidence of a systemic anti-inflammatory activity of phosphodiesterase type 5 (PDE5) inhibitors [9-12]: the concomitant decrease of systemic inflammation and improvement of DE symptoms in patients treated with tadalafil, 5 mg per day, should not come as an unexpected surprise [13]. Even acutely in a double blind, placebo-controlled, crossover study, a single-dose administration of sildenafil, 100 mg, significantly and persistently reduced fibrinogen, hs-CRP, hs-IL-6 (high-sensitivity interleukin-6), and Tumor Necrosis Factor-α (TNF-α) after 2 and 4 hours [14].

Based on these considerations, a rationale might exist for combining the anti-DE effect of PDE5 inhibitors with an attempt to modify the low-level inflammatory background that is associated with erectile dysfunctions. The goal would be to explore the possibility of enhancing the anti-DE action of PDE5 inhibitors. A pilot study was thus designed with a commercial dietary supplement complementing prescriptions of a standard PDE5 inhibitor; the small cohort of enrolled men with ED was representative of the subjects who come to attention in everyday andrology practice (full description of the dietary supplement in the "Methods" section, "4-month treatment protocol" subsection). The biologically active principles of natural origin of the dietary supplement combined both anti-inflammatory and microcirculation-protective activities.

METHODS

General design

Prospective cohort study in 14 subjects with a diagnosis of moderate to severe erectile dysfunction (age ranging from 49 and 77 years, mean age, 56.1 ± 5.3; range of basal IIEF-5 scores, 6-14; mean 9.1); at the end of the study, the final outcome the active sample was compared with the final outcome of a sample of historic controls treated only with sublingual sildenafil. Co-morbidities in the prospective cohort included mild LDL-cholesterol elevations in 2 subjects and mild nocturia (no more than 2 episodes per night) due to mild benign prostatic hyperplasia (echographically, about 50 mL) in 3 subjects.

The individual screening of candidate ED subjects included a standard andrological examination and interview with an emphasis on intake of drugs and concomitant diseases, sexology counseling, an evaluation of the metabolic (triglycerides, cholesterol levels, basal glycaemia), hormone (testosterone, prolactin, follicle-stimulating hormone, luteinizing hormone) and PSA (prostate specific antigen) profiles. The andrological examination also included a penile Doppler ultrasonography before and after intracavernous prostaglandin E_1 injection (mean alprostadil dose 10 μg, range based on anamnesis 7.5-12.5 μg).

Any echographic evidence of atherosclerosis or calcifications excluded enrollment. The normal serum testosterone ranges published in the last Endocrine Society paper[15] were used to discriminate between individuals eligible for enrollment in the study cohort and ineligible individual's candidate to treatment with testosterone gel.

All enrolled subjects filled a standard 5-question simplified International Index of Erectile Function (IIEF-5) questionnaire before beginning the treatment protocol and, on average, 7-10 days after the end of the 4-month treatment period.

Historic controls: sample of 25 moderate-to-severe ED subjects randomly selected from all the ED subjects currently attending the main author's ward or who had attended it over the last two years (age ranging from 50 and 74 years, mean age, 56.7 ± 5.8; IIEF-5 scores, range 6-9; basal mean, 7.5; distribution of age-related co-morbidities similar to the prospective cohort).

Controls and assessments

Endpoint: comparison of end-of-treatment vs. basal intra-cohort profiles of the IIEF-5 scores—i.e., comparison of the overall shape of frequency distributions. The pre- and after-treatment frequency distributions of sample IIEF-5 scores were compared for differences in skewness as an index of the overall profiles of ED severity. The study was conceived as exploratory in a field with poor previous information—i.e., the value of associating a standard 3-month PDE5 treatment with an attempt to modify the low-grade, ED-associated inflammatory background. Because of the exploratory nature of the study, historic controls were considered adequate to explore the value and added benefits, if any, of the combined anti-inflammatory/PDE5 treatment strategy. Only with the aim of qualitatively probing the work hypothesis, the final mean of the active cohort IIEF-5 scores was compared with the final mean of IIEF-5 scores in the sample of historic controls after three months of 25-mg sublingual sildenafil treatment.

4-month treatment protocol

First month: dietary supplement , one tablet per day in the morning for 30 days; second to fourth month: either sublingual sildenafil, 25 mg every other day in the morning while fasting, or dietary supplement, one tablet every other day in the morning alternating with sildenafil.

Statistics

Due to the exploratory nature of the study and the low

number of subjects enrolled, no statistical inference on means was planned and performed, and only a non-parametric Kolmogorov–Smirnov test was carried out. The aim was to assess for differences in the skewness of the one-dimensional (i.e., IIEF-5 scores) probability distributions of the active cohort. This was done by testing for differences between pre- and end-of-treatment overall ED severity in the cohort subjects under the conservative assumption of continuity. The low number of historic controls treated only with sublingual sildenafil prevented any reasonable statistical comparison with the final EEIF-5 scores in the active cohort.

Ethics

All study materials, including informed consent forms, study protocol and case report forms were peer-reviewed for ethical problems; the study followed the principles of the Declaration of Helsinki.

RESULTS

The fourteen men with ED symptoms of the prospective cohort were enrolled and treated as outpatients at the main author's Urology Operative Unit or at her private-practice office. All subjects had testosterone serum levels between 350 and 700 ng/dL (nanograms per deciliter). There was no difference in the distribution of age and co-morbidities likely to influence comparison.

At enrollment, crural Doppler fluximetry revealed a peak systolic velocity (PSV) compatible with impairment of the arterial influx into the cavernosum (PSV <25 cm/sec) [16] in only one subject and somewhat borderline in another one (cm/sec: centimeter per second); 50% of subjects had a "gray zone" PSV (25 to 35 cm/sec) [16]. Frankly veno-occlusive ED (persistent end-diastolic velocity >5 cm/sec during all phases of erection) [16] was never diagnosed and, as usual, venous competence could not be assessed in subjects with arterial insufficiency. Most of the patients showed penile engorgement and elongation with no rigidity.

Figure 1 summarizes the intra-cohort (before treatment vs. end of the study) outcomes of the study. There was a statistically significant shift towards higher IIEF-5 scores and increased left-skewness of the frequency distributions of IIEF-5 scores, with the median EEIF-5 scores increasing from, respectively, 8.5 before treatment to 21.0 (no more than mild ED) at the end of the study.

Qualitative comparison of the end-of-treatment median IIEF-5 scores, active cohort vs. historic controls treated only with sublingual sildenafil: 21.0 vs. 14.0, respectively.

DISCUSSION

Systemic inflammation has emerged as an important co-determinant of erectile dysfunction. Several mechanisms could explain this role. C-reactive protein (CRP), for instance, is known to inhibit endothelial nitric oxide synthase activity and to down-regulate the production of anti-inflammatory nitric oxide in human endothelial cells; CRP also increases the expression of endothelial P-selectin, E-selectin and vascular cell adhesion molecule-1 [5]. All these CRP activities converge on impairing endothelial reactivity and compromising erectile function because of reduced maximal vasodilatation and blood flow [5].

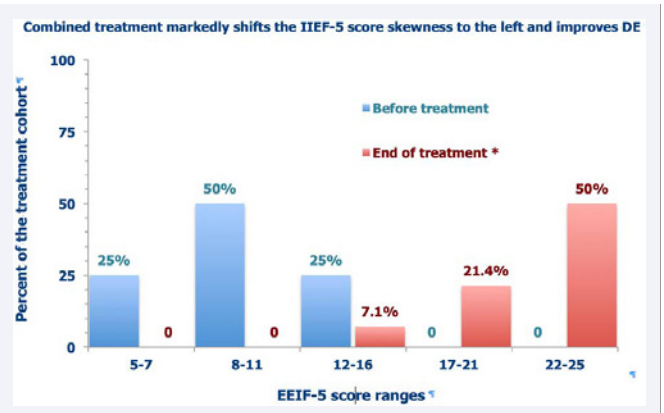

Figure 1 Frequency distributions of IIEF-5 scores in the treatment cohort at the beginning and at the end of the study.

* $p < 0.05$, end-of-treatment vs. before-treatment IIEF-5 scores profiles.

More recently, higher hs-CRP (high-sensitivity C-reactive protein) concentrations were shown to correlate with lower levels of total and free testosterone [17]. Independently of cardiovascular risk, low-grade systemic inflammation and subclinical endothelial dysfunction act as co-determinants of erectile dysfunction, as shown in young men with low risk of coronary heart disease [18]. Moreover, endothelial dysfunction has long been known to extend beyond corpora cavernosa in men with ED even before overt systemic vascular disease develop, always in agreement with a role for systemic inflammation in ED [19,20].

Trying to eliminate, or at least to attenuate, the low-grade systemic pro-inflammatory milieu that is associated with ED might enhance the efficacy of PDE5 inhibitors. That was the idea that led to conceive and design the exploratory study herein described.

The anti-inflammatory properties of a dietary supplement were deemed adequate for an exploratory investigation. This led the authors to identify and select a successful commercial product with distinctive anti-edema, anti-inflammatory, capillary-protective, and nitric oxide-normalizing properties. Pineapple bromelain is a powerful anti-inflammatory active principle. It is a mixture of sulfhydryl proteolytic enzymes that interferes with the expression of the TLR4 pro-inflammatory endothelial membrane receptor (TLR4: Toll-Like Receptor 4); bromelain also enhances the expression of the nuclear receptor PPAR that antagonizes the action of TLR4 (PPAR: Peroxisome Proliferator-Activated Receptor) [21]. Asiaticoside from *Centella asiatica* leaves dry extract [22], as well as highly purified turmeric curcumine and *Silybum marianum* (milk thistle) silymarin — the two latters acting as anti-oxidants — contribute to the anti-inflammatory efficacy of the selected dietary supplement [23,24]. Boswellic acids from frankincense and *Aesculus hippocastanum* (horse chestnut) escin protect capillaries and the microcirculation; both also reduce excessive pro-inflammatory nitric oxide levels [25,26].

The authors considered the uncontrolled cohort design of the study justified by the purely exploratory nature of the investigation. The preliminary one-month priming with the

anti-inflammatory and capillary-protective dietary supplement aimed at modifying the pro-inflammatory erectile dysfunctional milieu. Three months of alternating treatment with the anti-inflammatory dietary supplement and sublingual sildenafil followed the initial priming period; the comparison of the overall profiles of the cohort IIEF-5 scores was the efficacy endpoint. The general shape and skewness of the pre- and post-treatment IIEF-5 frequency distributions might be considered as an unusual and unspecific assessment parameter, yet the hypothesis-generating concept at the basis of the study justified this conservative choice.

Always because of the exploratory nature of the study, the authors deemed reasonable to compare the end-of-treatment IIEF-5 outcomes of the 1+3 course of treatment with sublingual sildenafil plus the inflammation-dampening dietary supplement with the IIEF-5 outcome of a similar 3-month course of PDE5 monotherapy in historic controls. Once again, this was considered justified because the study had no pretense of arriving at definitive conclusions, but was intended only as a preliminary probe of a new concept.

Unsurprisingly, the end-of-treatment intra-cohort IIEF-5 distribution was left-skewed compared with the basal distribution of IIEF-5 scores, with an overall increase of IIEF-5 scores and a lessened ED burden for the treatment cohort. The combined treatment appeared much successful with 50% of patients free of ED at the final follow-up visit (EEIF-5 score >22); the end-of-treatment median IIEF-5 score (21.0) was also very high. Did the background anti-inflammatory priming and co-treatment contribute to such a successful overall outcome? Did it enhance the PDE5 efficacy?

The comparison of the median end-of-treatment IIEF-5 score of the prospective cohort with the median end-of-treatment IIEF-5 score of the random sample of ED subjects treated only with sublingual sildenafil (14.0, compatible with persistently moderate ED) tentatively suggests this might indeed be the case. The study seems to support the general idea that associating a standard PDE5 inhibitor treatment with a background anti-inflammatory supplementation might be useful: possibly in all ED subjects, and most probably in ED subjects with any concomitant chronic inflammatory conditions. However, several biases of the study prevent all definitive conclusions.

Biases include a low number of ED subjects in the treatment cohort as well as a lack of prospective controls and randomization; proper controls were substituted by a small sample of historic controls. However, once again definitive conclusions were not the goal of this hypothesis-generating exploratory study.

CONCLUSIONS

Trying to cool down the ED-associated inflammatory milieu with an inexpensive dietary supplement that does not require prescription, aiming to enhance the efficacy of PDE5 inhibitors, was the research idea that led to this exploratory study. Even taking into consideration all the biases of an uncontrolled cohort study and historic controls, our investigation gives some support to the concept. Of course, further well-designed, unbiased investigations are warranted to confirm these preliminary suggestions.

DECLARATIONS

Ethics approval and consent to participate

All study materials, including informed consent forms, study protocol, and case report forms, were reviewed for ethical problems by the head physician of the Urology Operative Unit (Francesco Curto, himself an author) and the steering committee of the "Istituto G. Giglio" Foundation, Cefalù. The study followed the principles of the Declaration of Helsinki. Participating subjects would not be exposed to any foreseeable risk beyond those involved in the everyday andrological practice and the study protocol excluded any unusual procedure: for these reasons, the need for formal approval by an established Ethical Committee was waived.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available and are currently archived (with full personal details of all participating subjects) at the "Istituto G. Giglio" Foundation, Cefalù. All the datasets are anyway available (after conversion in anonymous form) from the corresponding author on reasonable request.

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AUTHORS' CONTRIBUTIONS

- HG, the main author, beyond directly contributing to the conception of the protocol, was responsible for explaining the aims of the study to the subjects who contacted her and the Istituto G. Giglio" Foundation for ED problems and who appeared suitable for enrollment. She was also personally responsible for getting the subjects' informed consent, for carrying out all procedures, investigations, and interviews, and for interpreting outcomes.
- FC, the second author, is the head physician of the Urology Operative Unit of the "Istituto G. Giglio" Foundation (Cefalù, Sicily, Italy). He made substantial contributions to the conception and design of the protocol; he also controlled all activities and respect of ethical rules and laws, and contributed to interpretation of outcomes.
- MR (corresponding author and manuscript submitter), an independent bioinformatics and statistics consultant with full medical qualifications and a special interest in male and female sexual medicine, made crucial contributions to the fine details of the study design. He also had full responsibility for identifying the conservative statistical strategy most suitable for a study with only exploratory ambitions, and for the analysis of data. His responsibilities also included drafting the manuscript and getting the approval and imprimatur of other authors.

All authors have approved the submitted version of the

manuscript and are personally accountable for their own contributions as well as for the accuracy and integrity of all the clinical work leading to the manuscript's submission to "Basic and Clinical Andrology".

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