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# Efficacy of vitamin E in the conservative treatment of Peyronie's disease: legend or reality? A controlled study of 70 cases

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## SUMMARY

The medical treatment is indicated in the development stage of Peyronie's disease (PD) for at least 1 year after diagnosis and whenever in case of penile pain. This research was conducted to demonstrate the possible effectiveness of vitamin E in PD treatment, whereas in the scientific literature this topic is much discussed. A total of 70 patients (age:26–69 years, mean: 54.1 ± 9.71) diagnosed with PD were enrolled in a conservative treatment. In addition to medical histories and physical examinations all patients underwent the following tests: International Index of Erectile Function (IIEF) questionnaire, penile ultrasound and photographic documentation, pain evaluation by a conventional 10-point pain scale Visual analogue pain scale (VAS). All 70 patients were divided into two different treatment groups: A and B, with different combinations of drugs: A = vitamin E + verapamil (injection + iontophoresis) + blueberries + propolis + topical diclofenac; B = verapamil (injection + iontophoresis) + blueberries + propolis + topical diclofenac. All patients were treated for 6 months after which they underwent the same follow-up tests as performed prior to the treatment. Intergroup analysis revealed statistically significant differences: in the vitamin E group the effective plaque size reduction was −50.2% whereas in the control group the reduction was −35.8% ($p = 0.027$). In group A the improvement of curvature occurred in 96.6% of the cases whereas in the control group B this occurred in 48.4% ($p = 0.0001$), moreover, the mean curvature decrease was respectively −12.25° and −6.73° ($p = 0.01$). IIEF score was significantly improved in group A patients with comorbidities and erectile dysfunction ($p = 0.025$). Increase in plaque size occurred only in the control group (17.1%) ($p = 0.032$). We can affirm that vitamin E can help to prevent the progression of PD. This study strongly supports the recommendation that the best approach for treating PD is multimodal therapy.

## INTRODUCTION

Peyronie's disease (PD) is a localized connective tissue disorder characterized by a fibrous inelastic plaque involving the tunica albuginea of the penis. Every defect in the tunica albuginea of the penis can deform the appearance and the static of the penis resulting in a possible penile curvature. Signs of PD are: penile curvature, pain, penile deformity, difficulty with coitus, shortening, hinging, narrowing and erectile dysfunction. Recent studies indicated a prevalence of 3.2–13.0% in adult men (Schwarzer *et al.*, 2001; Mulhall *et al.*, 2004; Dibenedetti *et al.*, 2011). Some authors have linked PD with Dupuytren's contracture, indicating coexistence of Dupuytren's disease in patients with PD (15.4–22.1%) (Chilton *et al.*, 1982; Nugteren *et al.*, 2011), while 15–30% of patients with Dupuytren's disease are affected by PD (Vanni & Bennett, 2009). Theaetiology of this fibrotic disease is not entirely known, although in recent years pathophysiological knowledge has evolved and new studies propose the penile trauma (micro- or macro-trauma) as cause of the disease (Devine *et al.*, 1997; Jarow & Lowe, 1997; Zargooshi, 2004). Deposition of fibrin determines the start of the response to wound healing with the secondary phlogistic process and production of inflammatory cytokines (TGF-beta-1 etc.) (Diegelmann, 1997; Somers & Dawson, 1997; Van de Water, 1997). Transforming growth factor-beta-1 (TGF-beta-1), in addition to inhibiting collagenase and promoting collagen synthesis, increases reactive oxygen species (ROS) levels (Gonzalez-Cadavid *et al.*, 2002). The release of cytokines and the overproduction of ROS contribute to determine the activation of Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which leads to the overproduction of collagen and the expression of

**Table 1** Clinical characteristics and basic demographics of PD patients in both groups

| Characteristics | Group vitamin E<br>Vitamin E + propolis + blueberry + verapamil + topical diclofenac | Control group<br>Propolis + blueberry + verapamil + topical diclofenac | Statistical analysis<br>*p*-value |
|---|---|---|---|
| Mean age (years) + SD | 53.8 ± 10.4 | 54.48 ± 8.7 | 0.768 (ANOVA) |
| Time since PD onset (months) + SD | 13.14 ± 4.81 | 13.85 ± 5.32 | 0.560 (ANOVA) |
| Mean plaque volume ($mm^3$) + SD | 1139.43 ± 1022.44 | 1150.50 ± 997.13 | 0.965 (ANOVA) |
| Plaque echogenicity/no. cases | | | |
| Hyperechoic | 17 | 18 | 0.811 ($\chi^2$ test) |
| Hypoechoic | 5 | 4 | 0.721 ($\chi^2$ test) |
| Isoechoic | 1 | 1 | 1.0 ($\chi^2$ test) |
| Inhomogeneous echogenicity | 12 | 12 | 1.0 ($\chi^2$ test) |
| Appearance of plaque calcification no. cases | 9 | 8 | 0.780 ($\chi^2$ test) |
| Mean calcification volume ($mm^3$) + SD | 191.25 ± 171.42 | 198.14 ± 153.68 | 0.932 (ANOVA) |
| Patients with erectile dysfunction no. cases | 13 | 12 | 0.803 ($\chi^2$ test) |
| Erectile function index—mean score + SD | 24.65 ± 3.17 | 24.31 ± 3.22 | 0.658 (ANOVA) |
| Penile pain during erection no. cases | 21 | 21 | 1.0 ($\chi^2$ test) |
| Penile pain—VAS—mean score + SD | 7.9 ± 2.26 | 7.38 ± 1.98 | 0.430 (ANOVA) |
| Penile curvature (mean degree) + SD | 30.16° ± 15.83 | 30.45° ± 12.81 | 0.933 (ANOVA) |
| Objective penile curvature/no. cases | 30/35 | 33/35 | 0.425 ($\chi^2$ test) |
| Lateral | 12 | 13 | 0.960 ($\chi^2$ test) |
| Dorsal | 8 | 9 | 0.956 ($\chi^2$ test) |
| Ventral | 1 | 1 | 0.945 ($\chi^2$ test) |
| Mixed dorso-lateral | 7 | 8 | 0.932 ($\chi^2$ test) |
| Mixed ventro-lateral | 2 | 2 | 0.921 ($\chi^2$ test) |
| Comorbidities, | no. cases | no. cases | *p*-value |
| Hypertension | 8 | 9 | 0.780 ($\chi^2$ test) |
| Dyslipidemia | 7 | 6 | 0.758 ($\chi^2$ test) |
| Ischaemic heart disease | 3 | 2 | 0.642 ($\chi^2$ test |
| Diabetes | 2 | 2 | 1.0 ($\chi^2$ test) |
| Hypotestosteronemia | 1 | 1 | 1.0 ($\chi^2$ test) |
| History of radical prostatectomy for prostatic cancer | 1 | 1 | 1.0 ($\chi^2$ test) |
| Chronic prostatitis | 1 | 1 | 1.0 ($\chi^2$ test) |
| History of urethritis ascribable to catheterization | 1 | 1 | 1.0 ($\chi^2$ test) |
| Cigarette smoking | 10 | 10 | 1.0 ($\chi^2$ test) |

genes on specific targets (fibrin, collagen, fibroblast growth factor-FGF, TGF-beta-1, inducible nitric oxide synthase-iNOS) (Sikka & Hellstrom, 2002; Paulis & Brancato, 2012). The overproduction of iNOS determines an excess of nitric oxide (NO) production with pathological consequences in the cavernosal penile tissue (Rajasekaran *et al.*, 2001). Current non-surgical therapies with varying success include: para-aminobenzoate, vitamin E, colchicine, tamoxifen, propolis, verapamil, interferons, collagenase, cortisone, pentoxifylline, superoxide dismutate, iontophoresis and extracorporeal shock wave therapy (Hauck *et al.*, 2006; Trost *et al.*, 2007; Taylor & Levine, 2008; Safarinejad *et al.*, 2010a). At present there is no gold standard available for the non-surgical therapy of PD, however, certainly the most appropriate approach should be multimodal therapy. Surgical treatment is indicated only when the patients have failed conservative therapy and the disease was stabilized for at least 3 months (although a 6–12 month period has also been suggested) (Jalkut *et al.*, 2003; Kendirci & Hellstrom, 2004; Hatzimouratidis *et al.*, 2012), and when the patients are unable to perform a sexual intercourse (ascribable to strong penile curvature or erectile dysfunction) (Hellstrom, 2009).

Vitamin E was the first oral therapy proposed for the treatment of PD (Scardino & Scott, 1949; Steinberg, 1951; Kunstmann, 1954); it is a potent antioxidant that is thought to reduce collagen deposits within the tunica albuginea. Vitamin E in addition interacts with hydroxyl radical (hydroxide, the more damaging ROS) donating a hydrogen atom to restore the molecule to normal inert state (Sikka & Hellstrom, 2002). A double-blinded, placebo-controlled, crossover study (Pryor & Farrell, 1983) showed no significant improvements in penile curvature or plaque size. Hauck *et al.* (2006) argued that, despite vitamin E being widely used, there is no evidence that it has a significant effect on the symptoms of PD, however, some studies have reported that vitamin E and its metabolites have an anti-inflammatory and anti-COX2 property (O'Leary *et al.*, 2004; Jang *et al.*, 2008). Possible toxicity caused by chronic intake of vitamin E has often been discussed in medical literature; however, regarding the toxicity-mortality rate referable to the accumulation of vitamin E, the latest meta-analysis has shown that this event does not seem to occur with doses up to 5 500 IU/daily (Abner *et al.*, 2011). A recently published study (Klein *et al.*, 2011) has found that a dietary supplementation with vitamin E significantly increases the risk of prostate cancer among healthy men; the vitamin E analysed in the study corresponds to a synthetic ester of vitamin E (all-rac-alpha-tocopheryl acetate). However, it is important to mention that other studies instead found no overall association between vitamin E supplement use and prostate cancer, furthermore vitamin E supplementation in smokers was associated with reduced risks of this disease (Kirsh *et al.*, 2006; Weinstein *et al.*, 2007; Wright *et al.*, 2007). The aim of this study was to determine the possible effectiveness of vitamin E in PD treatment, whereas in the scientific literature this topic is much discussed (Pryor & Farrell, 1983; Prieto Castro *et al.*, 2003; Hashimoto *et al.*, 2006; Hauck *et al.*, 2006; Safarinejad *et al.*, 2007).

Although the positive role of Verapamil in PD already has been established (Levine *et al.*, 1994; Rehman *et al.*, 1998; Bennett

**Table 2** Results after treatment

| Studied patterns | Vitamin E group Vitamin E + propolis + blueberry + verapamil + topical diclofenac | Control group Propolis + blueberry + verapamil + topical diclofenac | Statistical analysis *p*-value |
|---|---|---|---|
| Pain disappearance mean rate percentage/no. patients/total patients | 95.23 (20/21) | 80.95 (17/21) | 0.340 ($\chi^2$ test) |
| Success in reducing the plaque size mean rate percentage/no. patients/total patients | 97.14 (34/35) | 68.57 (24/35) | 0.004 ($\chi^2$ test) |
| Effective reduction in plaque size mean rate percentage + SD | −50.2 ± 22.62 | −35.8 ± 28.38 | 0.027 (ANOVA) |
| Disappearance of the plaque mean rate percentage/no. patients/total patients | 2.8 (1/35) | 0 (0/35) | 0.313 ($\chi^2$ test) |
| Increase of plaque size mean rate percentage/no. patients/total patients | 0 (0/35) | 17.14 (6/35) | 0.032 ($\chi^2$ test) |
| Success in reducing the calcification size mean rate percentage/no. patients/total patients | 100 (9/9) | 87.5 (7/8) | 0.951 ($\chi^2$ test) |
| Effective reduction in calcification size mean rate percentage + SD | −58.84 ± 27.31 | −28.21 ± 13.11 | 0.017 (ANOVA) |
| Disappearance of the penile calcification mean rate percentage/no. patients/total patients | 11.1 (1/9) | 0 (0/8) | 0.331 ($\chi^2$ test) |
| Increase of calcification size mean rate percentage/no. patients/total patients | 0 (0/9) | 12.5 (1/8) | 0.951 ($\chi^2$ test) |
| Improvement of penile curvature mean rate percentage/no. patients/total patients | 96.66 (29/30) | 48.48 (16/33) | 0.0001 ($\chi^2$ test) |
| Disappearance of the penile curvature mean rate percentage/no. patients/total patients | 16.66 (5/30) | 3.03 (1/33) | 0.158 ($\chi^2$ test) |
| Worsening of penile curvature mean rate percentage/no. patients/total patients | 0 (0/30) | 9.09 (3/33) | 0.271 ($\chi^2$ test) |
| Appearance of penile curvature mean rate percentage/no. patients/total patients | 0 (0/30) | 3.03 (1/33) | 0.336 ($\chi^2$ test) |
| Decrease of the penile curvature angle average−degrees + SD | −12.25° ± 7.75 | −6.73° ± 8.49 | 0.011 (ANOVA) |
| Percentage reduction of the penile curvature angle mean rate percentage + SD | −50.02 ± 29.59 | −20.70 ± 24.68 | 0.000 (ANOVA) |
| Restoration of rigid erection mean rate percentage/no. patients/total patients | 69.23 (9/13) | 41.66 (5/12) | 0.325 ($\chi^2$ test) |
| Improvement of penile rigidity mean rate percentage/no. patients/total patients | 74.28 (26/35) | 60.0 (21/35) | 0.308 ($\chi^2$ test) |
| Effective improvement of erectile function index score in different classes of patients: ↓ | | | |
| In total patients with PD and erectile dysfunction IIEF−mean score + SD + (no. patients) | +5.07 ± 1.63 (13) | +3.83 ± 0.79 (12) | 0.025 (ANOVA) |
| In patients with PD, erectile dysfunction associated with comorbidities IIEF−mean score + SD + (no. patients) | +5.09 ± 1.72 (11) | +3.5 ± 0.7 (8) | 0.025 (ANOVA) |
| In patients with PD, comorbidities (excluding erectile dysfunction) IIEF−mean score + SD + (no. patients) | +0.7 ± 0.45 (10) | +0.28 ± 0.45 (14) | 0.036 (ANOVA) |
| In patients with PD, excluding erectile dysfunction and comorbidities IIEF − mean score + SD + (no. patients) | +0.58 ± 0.64 (12) | +0.66± 0.66 (9) | 0.783 (ANOVA) |

*et al.*, 2007; Cavallini *et al.*, 2007), many recent studies have demonstrated the efficacy of several substances with anti-oxidative activity (propolis, carnitine, pentoxifylline, coenzyme Q10, blueberry flavonoids etc.) in the treatment of PD (Cavallini *et al.*, 2002; Safarinejad, 2010b; Safarinejad *et al.*, 2010a; Paulis *et al.*, 2012). Verapamil reduces the proliferation of fibroblasts and the local production of extracellular matrix (by fibroblasts); it also increases the local activity of collagenase and it affects the cytokine regulation of fibroblasts reducing the excess production of fibrogenic cytokines (Taylor & Levine, 2008).

The component of propolis, caffeic acid phenethyl ester (CAPE) inhibits NF-κB activity and the production of interleukins (Natarajan *et al.*, 1996; Marquez *et al.*, 2004; Song *et al.*, 2008). Chrysin, another component of propolis, inhibits the release of nitric oxide, the production of TNF-alpha, IL-1β and the expressions of cyclooxygenase-2 (COX-2) and inducible iNOS (Ha *et al.*, 2010). Blueberry anthocyanins inhibit iNOS, COX-2 expression, NF-κB activation (Karlsen *et al.*, 2007; Wang *et al.*, 2008); moreover, they protect endothelial cells against peroxynitrite-induced apoptosis (Serraino *et al.*, 2003; Paixão *et al.*, 2011).

## MATERIALS & METHODS

This is a controlled study, designed to investigate the possible benefits of vitamin E in patients with PD enrolled for a non-surgical treatment. Between January 2010 and February 2012, 70 patients with PD were selectioned and enrolled for a conservative treatment. All patients were informed of the possible surgical procedure. However, none of them wished to undergo surgery.

Exclusion criteria were as follows: any medical treatment for sexual dysfunction, before or during the study; supplementation with traditional herbs or vitamins in the previous 6 months; stabilized Peyronie's disease; penile curvature that does not allow sexual intercourse; patients with atrioventricular (AV) conduction defects; patients aged greater than or equal to 70 years (to avoid possible potential negative effects of Verapamil on atrio-ventricular conduction)( Echizen *et al.*, 1985; Busse *et al.*, 2006). From the original 92 patients, 22 cases were initially excluded from the study and treatment for the following reasons: two patients with stabilized PD; six patients who had taken PDE-5 inhibitors in the 6 months prior to study; one patient with first-degree atrioventricular block and two old patients (70–73 years); a total of 11 patients that did not guarantee the statistical homogeneity of both treatment groups for various reasons (comorbidity, presence of erectile dysfunction, type and degree of penile curvature, plaque echogenicity, plaque volume, calcification size); these 22 patients were still treated, but we did not include their results in this study.

**Main outcome measures:**

in addition to medical history and physical examinations, all 70 patients underwent the following tests: dynamic penile ultrasound, penile X-ray (only in case of 'shadow-cone' during the ultrasound study). The penile curvature was measured by taking a photograph during maximum erection. Penile pain was evaluated by a conventional 10-point Visual analogue pain scale (VAS). All patients completed the questionnaire International Index of Erectile Function (IIEF) (Rosen *et al.*, 1997); the answers that we evaluated were the questions 1–5 and 15, which specifically address the aspects of Erectile Function (IIEF-EF normal score: 26–30). Patients who had a total score of less than 26 were identified as having erectile dysfunction.

All patients were treated for a total time of 6 months and then underwent the same tests as performed prior to the treatment.

 

**Table 3** Intergroup analysis of efficacy of used drugs according to severity of the disease: plaque size

| Studied patterns | Vitamin E group Vitamin E + propolis + blueberry + verapamil + topical diclofenac | Control group Propolis + blueberry + verapamil + topical diclofenac | Statistical analysis *p*-value |
|---|---|---|---|
| Penile plaques with volume up to 500 $mm^3$ | | | |
| Pain disappearance mean rate percentage/no. patients/total patients | 100 (5/5) | 85.71 (6/7) | 0.377 ($\chi^2$ test) |
| Success in reducing the plaque size mean rate percentage/ no. patients/total patients | 100 (9/9) | 70.0 (7/10) | 0.245 ($\chi^2$ test) |
| Effective reduction in plaque size mean rate percentage + SD | −59.88 ± 23.68 | −50.06 ± 33.44 | 0.491 (ANOVA) |
| Disappearance of the plaque mean rate percentage/no. patients/total patients | 0 (0/9) | 0 (0/10) | 1.0 ($\chi^2$ test) |
| Increase of plaque size mean rate percentage/ no. patients/total patients | 0 (0/9) | 20.0 (2/10) | 0.503 ($\chi^2$ test) |
| Success in reducing the calcification size mean rate percentage/no. patients/total patients | 100 (2/2) | 100 (1/1) | 1.0 ($\chi^2$ test) |
| Effective reduction in calcification size mean rate percentage + SD | −84.25 ± 15.05 | −20.0 ± 0 | 0.178 (ANOVA) |
| Disappearance of the penile calcification mean rate percentage/no. patients/total patients | 0 (0/2) | 0 (0/1) | 1.0 ($\chi^2$ test) |
| Increase of calcification size mean rate percentage/no. patients/total patients | 0 (0/2) | 0 (0/1) | 1.0 ($\chi^2$ test) |
| Improvement of penile curvature mean rate percentage/no. patients/total patients | 100 (8/8) | 40.0 (4/10) | 0.029 ($\chi^2$ test) |
| Disappearance of the penile curvature mean rate percentage/no. patients/total patients | 25.0 (2/8) | 0 (0/10) | 0.356 ($\chi^2$ test) |
| Worsening of penile curvature mean rate percentage/no. patients/total patients | 0 (0/8) | 10.0 (1/10) | 0.357 ($\chi^2$ test) |
| Appearance of penile curvature mean rate percentage/no. patients/total patients | 0 (0/8) | 0 (0/10) | 1.0 ($\chi^2$ test) |
| Decrease of the penile curvature angle average−degrees + SD | −7.5° ± 2.5 | −5.0° ± 5.77 | 0.276 (ANOVA) |
| Percentage reduction of the penile curvature angle mean rate percentage + SD | −51.18 ± 30.11 | −15.43 ± 18.47 | 0.009 (ANOVA) |
| Restoration of rigid erection mean rate percentage/no. patients/total patients | 100 (1/1) | 0 (0/2) | 0.333 ($\chi^2$ test) |
| Penile plaques with volume above 500 $mm^3$ | | | |
| Pain disappearance mean rate percentage/no. patients/total patients | 93.75 (15/16) | 78.57 (11/14) | 0.495 ($\chi^2$ test) |
| Success in reducing the plaque size mean rate percentage/no. patients/total patients | 96.15 (25/26) | 68 (17/25) | 0.023 ($\chi^2$ test) |
| Effective reduction in plaque size mean rate percentage + SD | −46.85 ± 21.24 | −30.37 ± 24.07 | 0.016 (ANOVA) |
| Disappearance of the plaque mean rate percentage/no. patients/total patients | 3.84 (1/26) | 0 (0/25) | 0.322 ($\chi^2$ test) |
| Increase of plaque size mean rate percentage/no. patients/total patients | 0 (0/26) | 16.0 (4/25) | 0.05 ($\chi^2$ test) |
| Success in reducing the calcification size mean rate percentage/no. patients/total patients | 100 (7/7) | 85.71 (6/7) | 0.299 ($\chi^2$ test) |
| Effective reduction in calcification size mean rate percentage + SD | −51.58 ± 25.64 | −29.57 ± 13.69 | 0.087 (ANOVA) |
| Disappearance of the penile calcification mean rate percentage/no. patients/total patients | 14.28 (1/7) | 0 (0/7) | 0.299 ($\chi^2$ test) |
| Increase of calcification size mean rate percentage/no. patients/total patients | 0 (0/7) | 14.28 (1/7) | 0.299 ($\chi^2$ test) |
| Improvement of penile curvature mean rate percentage/no. patients/total patients | 95.45 (21/22) | 52.17 (12/23) | 0.003 ($\chi^2$ test) |
| Disappearance of the penile curvature mean rate percentage/no. patients/total patients | 13.63 (3/22) | 4.34 (1/23) | 0.568 ($\chi^2$ test) |
| Worsening of penile curvature mean rate percentage/no. patients/total patients | 0 (0/22) | 8.69 (2/23) | 0.489 ($\chi^2$ test) |
| Appearance of penile curvature mean rate percentage/no. patients/total patients | 0 (0/22) | 4.34 (1/23) (+5°) | 0.322 ($\chi^2$ test) |
| Decrease of the penile curvature angle average−degrees + SD | −13.97° ± 8.27 | −7.47 ± 9.32 | 0.019 (ANOVA) |
| Percentage reduction of the penile curvature angle mean rate percentage + SD | −49.60 ± 29.39 | −22.96 ± 26.59 | 0.003 (ANOVA) |
| Restoration of rigid erection mean rate percentage/no. patients/total patients | 66.66 (8/12) | 50 (5/10) | 0.665 ($\chi^2$ test) |

All 70 selected patients were randomly assigned to two different groups (A and B) and then treated with different combinations of drugs:

(A) Vitamin E group: Vitamin E 600 mg/oral/daily (D-Alpha Tocopherol) + Verapamil injection (peri-lesional) 10 mg/ every 2 weeks (12 total injections – the first injection 5 mg) + iontophoresis with 5 mg daily (excluding the day of injection) + blueberries 160 mg/oral/daily + propolis 600 mg/oral/daily (on an empty stomach to facilitate absorption) + topical Diclofenac sodium 4% gel/twice a day.

(B) Control group: Verapamil injection (peri-lesional) 10 mg/ every 2 weeks (12 total injections – the first injection 5 mg) + iontophoresis with 5 mg daily (excluding the day of injection) + blueberries 160 mg/oral/daily + propolis 600 mg/oral/daily (on an empty stomach to facilitate absorption) + topical Diclofenac sodium 4% gel/twice a day.

To avoid episodes of hypotension or disorders in AV conduction in the case of a hypertensive patient treated with calcium channel blockers, it was suggested that the patient not take the dose of such drugs on the day of the penile injection. The number of these patients was the same in both groups (two cases treated with nifedipine or amlodipine). Iontophoresis was used placing the drug Verapamil (5 mg) on the positive pole with 4 mA output and for a duration of 20 min/day. The blueberries administered were a pharmaceutical preparation containing blueberry extract (36% anthocyanosides) associated with propolis, which have already demonstrated good efficacy (Lemourt Oliva *et al.*, 1998; Lemourt Oliva *et al.*, 2003a, 2003b; Lemourt Oliva *et al.*, 2005; Paulis *et al.*, 2012) in treating the disease by reducing plaque size and penile curvature.

The results of this study were subject to statistical analysis using Primer of biostatistics (by Stanton A. Glantz) software. A statistically significant consideration was when the *p*-value was less than 0.05. This work was carried out in accordance with the Helsinki Declaration of 1975 as revised in 1983.

## RESULTS

The study involved 70 patients (mean age = 54.1 ± 9.7 years; range 26–69 years). In most cases (90%) patients reported a penile curvature (63/70 cases). Penile pain was present in 42 patients (60%) and the mean score (VAS) was 7.7 (± 2.1 SD). Erectile dysfunction was present in 25 cases (35.7%).

The two different treated groups are homogeneous for a statistical analysis of results (patient age, diseases onset, presence and

**Table 4** Analysis (within each group) of efficacy of used drugs according to severity of the disease: plaque size

| Studied patterns | Penile plaques with volume up to 500 $mm^3$ | Penile plaques with volume above 500 $mm^3$ | Statistical analysis *p*-value |
|---|---|---|---|
| Vitamin E group | | | |
| (Vitamin E + propolis + blueberry + verapamil + topical diclofenac) | | | |
| Pain disappearance mean rate percentage/no. patients/total patients | 100 (5/5) | 93.75 (15/16) | 0566 ($\chi^2$ test) |
| Success in reducing the plaque size mean rate percentage/no. patients/total patients | 100 (9/9) | 96.15 (25/26) | 0.550 ($\chi^2$ test) |
| Effective reduction in plaque size mean rate percentage + SD | −59.88 ± 23.68 | −46.85 ± 21.24 | 0.133 (ANOVA) |
| Disappearance of the plaque mean rate percentage/no. patients/total patients | 0 (0/9) | 3.84 (1/26) | 0.550 ($\chi^2$ test) |
| Increase of plaque size mean rate percentage/no. patients/total patients | 0 (0/9) | 0 (0/26) | 1.0 ($\chi^2$ test) |
| Success in reducing the calcification size mean rate percentage/no. patients/total patients | 100 (2/2) | 100 (7/7) | 1.0 ($\chi^2$ test) |
| Effective reduction in calcification size mean rate percentage + SD | −84.25 ± 15.05 | −51.58 ± 25.64 | 0.139 (ANOVA) |
| Disappearance of the penile calcification mean rate percentage/no. patients/total patients | 0 (0/2) | 14.28 (1/7) | 0.570 ($\chi^2$ test) |
| Increase of calcification size mean rate percentage/no. patients/total patients | 0 (0/2) | 0 (0/7) | 1.0 ($\chi^2$ test) |
| Improvement of penile curvature mean rate percentage/no. patients/total patients | 100 (8/8) | 95.45 (21/22) | 0.539 ($\chi^2$ test) |
| Disappearance of the penile curvature mean rate percentage/no. patients/total patients | 25.0 (2/8) | 13.63 (3/22) | 0.853 ($\chi^2$ test) |
| Worsening of penile curvature mean rate percentage/no. patients/total patients | 0 (0/8) | 0 (0/22) | 1.0 ($\chi^2$ test) |
| Appearance of penile curvature mean rate percentage/no. patients/total patients | 0 (0/8) | 0 (0/22) | 1.0 ($\chi^2$ test) |
| Decrease of the penile curvature angle average–degrees + SD | −7.5° ± 2.5 | −13.97° ± 8.27 | 0.040 (ANOVA) |
| Percentage reduction of the penile curvature angle mean rate percentage + SD | −51.18 ± 30.11 | −49.60 ± 29.39 | 0.898 (ANOVA) |
| Restoration of rigid erection mean rate percentage/no. patients/total patients | 100 (1/1) | 66.66 (8/12) | 0.487 ($\chi^2$ test) |
| Control group | | | |
| (Propolis + blueberry + verapamil + topical diclofenac) | | | |
| Pain disappearance mean rate percentage/no. patients/total patients | 85.71 (6/7) | 78.57 (11/14) | 0.694 ($\chi^2$ test) |
| Success in reducing the plaque size mean rate percentage/no. patients/total patients | 70.0 (7/10) | 68.0 (17/25) | 0.908 ($\chi^2$ test) |
| Effective reduction in plaque size mean rate percentage + SD | −50.06 ± 33.44 | −30.37 ± 24.07 | 0.088 (ANOVA) |
| Disappearance of the plaque mean rate percentage /no. patients/total patients | 0 (0/10) | 0 1(0/25) | 1.000 ($\chi^2$ test) |
| Increase of plaque size mean rate percentage/no. patients/total patients | 20.0 (2/10) | 16.0 (4/25) | 0.776 ($\chi^2$ test) |
| Success in reducing the calcification size mean rate percentage/no. patients/total patients | 100 (1/1) | 85.71 (6/7) | 0.686 ($\chi^2$ test) |
| Effective reduction in calcification size mean rate percentage + SD | −20.0 ± 0 | −29.57 ± 13.69 | 0.546 (ANOVA) |
| Disappearance of the penile calcification mean rate percentage/no. patients/total patients | 0 (0/1) | 0 (0/7) | 1.000 ($\chi^2$ test) |
| Increase of calcification size mean rate percentage/no. patients/total patients | 0 (0/1) | 14.28 (1/7) | 0.686 ($\chi^2$ test) |
| Improvement of penile curvature mean rate percentage/no. patients/total patients | 40.0 (4/10) | 52.17 (12/23) | 0.791 ($\chi^2$ test) |
| Disappearance of the penile curvature mean rate percentage/no. patients/total patients | 0 (0/10) | 4.34 (1/23) | 0.503 ($\chi^2$ test) |
| Worsening of penile curvature mean rate percentage/no. patients/total patients | 10.0 (1/10) | 8.69 (2/23) | 0.904 ($\chi^2$ test) |
| Appearance of penile curvature mean rate percentage/no. patients/total patients | 0 (0/10) | 4.34 (1/23) (+ 5°) | 0.503 ($\chi^2$ test) |
| Decrease of the penile curvature angle average–degrees + SD | −5.0° ± 5.77 | −7.47° ± 9.32 | 0.468 (ANOVA) |
| Percentage reduction of the penile curvature angle mean rate percentage + SD | −15.43 ± 18.47 | −22.96 ± 26.59 | 0.448 (ANOVA) |
| Restoration of rigid erection mean rate percentage/no. patients/total patients | 0 (0/2) | 50 (5/10) | 0.469 ($\chi^2$ test) |

intensity of penile pain, plaque volume, calcification size, degree of curvature, presence or absence of erectile dysfunction and comorbidities). In all cases when calcification was present, it did not exist in the whole area of the plaque, but was only present in small part, confirming that the disease was in the progressive phase (and it was not stabilized).

Moreover, in all cases, in addition to calcification and fibrous plaque was present penile pain, typical of progressive phase. In these cases VAS score was between 7 and 10, denoting active phase of PD.

Clinical characteristics and basic demographics related to the two groups of PD patients are listed in Table 1.

### Evaluation of treatment results

Intergroup analysis revealed statistically significant differences in terms of effective plaque size reduction, improvement of curvature and effective improvement of erectile function index score (see Table 2). In the vitamin E-treated group the success in reducing plaque size was 97.14% whereas in the control group the success was 68.57% ($p = 0.004$). In the vitamin E-treated group the effective plaque size reduction was −50.2% whereas in the control group the reduction was −35.8% ($p = 0.027$). In the vitamin E group the effective calcification size reduction was −58.8% whereas in the control group the reduction was −28.21% ($p = 0.017$). Furthermore, in group A the improvement of curvature occurred in 29 patients (96.6%) whereas in the control group this occurred only in 16 patients (48.4%) ($p = 0.0001$), moreover, the mean curvature decrease was −12.25° and −6.73° respectively ($p = 0.01$). Although the penile rigidity improvement percentage was not statistically significant between the two groups, IIEF score was significantly improved in group A patients with comorbidities and erectile dysfunction ($p = 0.025$) (Table 2). Furthermore, the increase in plaque size occurred only in the control group (six cases = 17.1%) and this result was also statistically significant ($p = 0.032$).

### Analysis of the efficacy of used drugs according to severity of the disease

In relation to the 'plaque size', intergroup analysis (Vit E group vs. Control group) revealed statistically significant differences when the plaques were greater above 500 $mm^3$: 'plaque size reduction' and 'improvement of curvature' respectively $p = 0.016$ and $p = 0.003$ (Table 3) (see Tables 3–6). In the case of smaller plaques with volume up to 500 $mm^3$, intergroup analysis revealed statistically significant differences only with regard to the 'improvement of curvature' ($p = 0.029$). However, we think that it was caused by the shrinkage of the statistical sample. Overall, there were no significant differences in the comparison of the

 

**Table 5** Analysis (within each group) of efficacy of used drugs according to severity of the disease: degree of penile curvature

| Studied patterns | Penile curvature angle not exceeding 25 degrees (angle $\leq$ 25°) | Penile curvature angle exceeding 25 and not exceeding 45 degrees (angle > 25 $\leq$ 45°) | Statistical analysis *p*-value |
|---|---|---|---|
| Vitamin E group | | | |
| (Vitamin E + propolis + blueberry + verapamil + topical diclofenac) | | | |
| Pain disappearance mean rate percentage/no. patients/total patients | 87.5 (7/8) | 100 (11/11) | 0.421 ($\chi^2$ test) |
| Success in reducing the plaque size mean rate percentage/no. patients/total patients | 100 (13/13) | 94.1 (16/17) | 0.373 ($\chi^2$ test) |
| Effective reduction in plaque size mean rate percentage + SD | −58.41 ± 24.11 | −45.85 ± 20.23 | 0.132 (ANOVA) |
| Disappearance of the plaque mean rate percentage/no. patients/total patients | 7.69 (1/13) | 0 (0/17) | 0.891 ($\chi^2$ test) |
| Increase of plaque size mean rate percentage/no. patients/total patients | 0 (0/13) | 0 (0/17) | 1.0 ($\chi^2$ test) |
| Success in reducing the calcification size mean rate percentage/no. patients/total patients | 100 (3/3) | 100 (4/4) | 1.0 ($\chi^2$ test) |
| Effective reduction in calcification size mean rate percentage + SD | −88.76 ± 15.39 | −51.52 ± 17.58 | 0.033 (ANOVA) |
| Disappearance of the penile calcification mean rate percentage/no. patients/total patients | 33.33 (1/3) | 0 (0/4) | 0.876 ($\chi^2$ test) |
| Increase of calcification size mean rate percentage/no. patients/total patients | 0 (0/3) | 0 (0/4) | 1.0 ($\chi^2$ test) |
| Improvement of penile curvature mean rate percentage/no. patients/total patients | 92.3 (12/13) | 100 (17/17) | 0.891 ($\chi^2$ test) |
| Disappearance of the penile curvature mean rate percentage/no. patients/total patients | 30.76 (4/13) | 5.88 (1/17) | 0.137 ($\chi^2$ test) |
| Worsening of penile curvature mean rate percentage/no. patients/total patients | 0 (0/13) | 0 (0/17) | 1.0 ($\chi^2$ test) |
| Decrease of the penile curvature angle average–degrees + SD | −9.8° ± 5.92 | −14.11° ± 8.44 | 0.128 (ANOVA) |
| Percentage reduction of the penile curvature angle mean rate percentage + SD | −65.76 ± 28.54 | −37.75 ± 24.42 | 0.007 (ANOVA) |
| Restoration of rigid erection mean rate percentage/no. patients/total patients | 50.0 (1/2) | 80.0 (8/10) | 0.454 ($\chi^2$ test) |
| Control group | | | |
| (Propolis + blueberry + verapamil + topical diclofenac) | | | |
| Pain disappearance mean rate percentage/no. patients/total patients | 85.71 (6/7) | 78.57 (11/14) | 0.694 ($\chi^2$ test) |
| Success in reducing the plaque size mean rate percentage/no. patients/total patients | 60.0 (6/10) | 73.91 (17/23) | 0.698 ($\chi^2$ test) |
| Effective reduction in plaque size mean rate percentage + SD | −40.85 ± 32.85 | −35.11 ± 26.89 | 0.647 (ANOVA) |
| Disappearance of the plaque mean rate percentage/no. patients/total patients | 0 (0/10) | 0 (0/23) | 1.0 ($\chi^2$ test) |
| Increase of plaque size mean rate percentage/no. patients/total patients | 30.0 (3/10) | 8.69 (2/23) | 0.298 ($\chi^2$ test) |
| Success in reducing the calcification size mean rate percentage/no. patients/total patients | 100 (1/1) | 85.71 (6/7) | 0.686 ($\chi^2$ test) |
| Effective reduction in calcification size mean rate percentage + SD | −43.4 ± 0 | −27.18 ± 12.66 | 0.289 (ANOVA) |
| Disappearance of the penile calcification mean rate percentage/no. patients/total patients | 0 (0/1) | 0 (0/7) | 1.0 ($\chi^2$ test) |
| Increase of calcification size mean rate percentage/no. patients/total patients | 0 (0/1) | 14.28 (1/7) | 0686 ($\chi^2$ test) |
| Improvement of penile curvature mean rate percentage/no. patients/total patients | 40.0 (4/10) | 52.17 (12/23) | 0.791 ($\chi^2$ test) |
| Disappearance of the penile curvature mean rate percentage/no. patients/total patients | 20.0 (2/10) | 0 (0/23) | 0.085 ($\chi^2$ test) |
| Worsening of penile curvature mean rate percentage/no. patients/total patients | 0 (0/10) | 13.04 (3/23) | 0.589 ($\chi^2$ test) |
| Decrease of the penile curvature angle average–degrees + SD | −4.7° ± 7.6 | −7.75 ± 8.72 | 0.355 (ANOVA) |
| Percentage reduction of the penile curvature angle mean rate percentage + SD | −28.5 ± 39.5 | −18.74 ± 18.81 | 0.363 (ANOVA) |
| Restoration of rigid erection mean rate percentage/no. patients/total patients | 100 (3/3) | 25.0 (2/8) | 0.122 ($\chi^2$ test) |

results in the same treatment group (A or B) (plaques-up to 500 $mm^3$ vs. plaques-above 500 $mm^3$). Nevertheless, only for the 'decrease of penile curvature angle', in A group there was a significant difference (Table 4), but after analysing the comparison results for the 'percentage reduction of penile curvature', a significant improvement of curvature was not confirmed (Table 4).

The analysis (within each group) of the efficacy of used drugs according to 'degree of penile curvature' has revealed that patients with mild degree of curvature responded better only in 'vitamin E group' (Table 5). Intergroup analysis of efficacy of used drugs according to 'degree of penile curvature' confirmed that significantly better results were obtained in A group (Table 6).

Significant drug-related adverse effects did not occur in the two studied groups and no patient discontinued the treatment because of side effects. No cases of hypotension or heart rhythm disorder occurred during the treatment.

## DISCUSSION AND CONCLUSIONS

In our study, all patients had nostabilized disease. All patients were informed of the possible surgical procedure alternative to the conservative medical treatment. However, all the patients have ruled out the possibility of a surgical operation. We think that surgery is indicated only in patients with stabilized disease (Kendirci & Hellstrom, 2004). Medical treatment is indicated in the development stage of PD (Jalkut *et al.*, 2003; Hauck *et al.*, 2006; Taylor & Levine, 2008; Hellstrom, 2009). This recommendation should also take into consideration the results of this study. However, surgical treatment is indicated only when the patients have failed to respond to the conservative therapy and in case of the disease stabilized (Jalkut *et al.*, 2003; Kendirci & Hellstrom, 2004; Hatzimouratidis *et al.*, 2012) and when the patients are unable to perform a sexual intercourse (ascribable to strong penile curvature or erectile dysfunction) (Hellstrom, 2009). In the present study, after a 6-month treatment no patient needed surgical therapy. The entire medical treatment had a cost of $1677 for each patient included in group A ($9.3/daily), whereas in group B patients it was $1541 for each patient ($8.5/daily). Objectively, the total cost of 6 months of treatment (even if repeated) was less expensive than surgical procedure. Vitamin E is commonly used to treat PD because of its antioxidant and antifibrotic effects, however, several studies have reported that vitamin E is ineffective to treat PD (Pryor & Farrell, 1983; Hashimoto *et al.*, 2006; Hauck *et al.*, 2006). Although vitamin E monotherapy showed no effects as compared to placebo other studies (Prieto Castro *et al.*, 2003; Safarinejad *et al.*, 2007) reported better results when vitamin E was administered in combination with another substance respectively propionyl-L-carnitine and colchicine, in the treatment of PD. Our results show that vitamin E with therapeutic dose, in combination with propolis, blueberry, Verapamil and topical Diclofenac, is very

**Table 6** Intergroup analysis of efficacy of used drugs according to severity of the disease: degree of penile curvature

| Studied patterns | Vitamin E group Vitamin E + propolis + blueberry + verapamil + topical diclofenac | Control group Propolis + blueberry + verapamil + topical diclofenac | Statistical analysis *p*-value |
|---|---|---|---|
| Penile curvature angle not exceeding 25 degrees (angle $\leq$ 25°) | | | |
| Pain disappearance mean rate percentage/no. patients/total patients | 87.5 (7/8) | 85.71 (6/7) | 0.919 ($\chi^2$ test) |
| Success in reducing the plaque size mean rate percentage/no. patients/total patients | 100 (13/13) | 60.0 (6/10) | 0.023 ($\chi^2$ test) |
| Effective reduction in plaque size mean rate percentage + SD | −58.41 ± 24.11 | −40.85 ± 32.85 | 0.187 (ANOVA) |
| Disappearance of the plaque mean rate percentage/no. patients/total patients | 7.69 (1/13) | 0 (0/10) | 0.369 ($\chi^2$ test) |
| Increase of plaque size mean rate percentage/no. patients/total patients | 0 (0/13) | 30.0 (3/10) | 0.135 ($\chi^2$ test) |
| Success in reducing the calcification size mean rate percentage/no. patients/total patients | 100 (3/3) | 100 (1/1) | 1.0 ($\chi^2$ test) |
| Effective reduction in calcification size mean rate percentage + SD | −88.76 ± 15.39 | −43.4 ± 0 | 0.125 (ANOVA) |
| Disappearance of the penile calcification mean rate percentage/no. patients/total patients | 33.33 (1/3) | 0 (0/1) | 0.505 ($\chi^2$ test) |
| Increase of calcification size mean rate percentage/no. patients/total patients | 0 (0/3) | 0 (0/1) | 1.0 ($\chi^2$ test) |
| Improvement of penile curvature mean rate percentage/no. patients/total patients | 92.3 (12/13) | 40.0 (4/10) | 0.024 ($\chi^2$ test) |
| Disappearance of the penile curvature mean rate percentage/no. patients/total patients | 30.76 (4/13) | 20.0 (2/10) | 0.917 ($\chi^2$ test) |
| Worsening of penile curvature mean rate percentage/no. patients/total patients | 0 (0/13) | 0 (0/10) | 1.0 ($\chi^2$ test) |
| Decrease of the penile curvature angle average–degrees + SD | −9.8° ± 5.92 | −4.7° ± 7.6 | 0.084 (ANOVA) |
| Percentage reduction of the penile curvature angle mean rate percentage + SD | −65.76 ± 28.54 | −28.5 ± 39.5 | 0.016 (ANOVA) |
| Restoration of rigid erection mean rate percentage/no. patients/total patients | 50.0 (1/2) | 100 (3/3) | 0.400 ($\chi^2$ test) |
| Penile curvature angle exceeding 25 and not exceeding 45 degrees (angle > 25 $\leq$ 45°) | | | |
| Pain disappearance mean rate percentage/no. patients/total patients | 100 (11/11) | 78.57 (11/14) | 0.230 ($\chi^2$ test) |
| Success in reducing the plaque size mean rate percentage/no. patients/total patients | 94.1 (16/17) | 73.91 (17/23) | 0.214 ($\chi^2$ test) |
| Effective reduction in plaque size mean rate percentage + SD | −45.85 ± 20.23 | −35.11 ± 26.89 | 0.181 (ANOVA) |
| Disappearance of the plaque mean rate percentage/no. patients/total patients | 0 (0/17) | 0 (0/23) | 1.0 ($\chi^2$ test) |
| Increase of plaque size mean rate percentage/no. patients/total patients | 0 (0/17) | 8.69 (2/23) | 0.498 ($\chi^2$ test) |
| Success in reducing the calcification size mean rate percentage/no. patients/total patients | 100 (4/4) | 85.71 (6/7) | 0.427 ($\chi^2$ test) |
| Effective reduction in calcification size mean rate percentage + SD | −51.52 ± 17.58 | −27.18 ± 12.66 | 0.033 (ANOVA) |
| Disappearance of the penile calcification mean rate percentage/no. patients/total patients | 0 (0/4) | 0 (0/7) | 1.0 ($\chi^2$ test) |
| Increase of calcification size mean rate percentage/no. patients/total patients | 0 (0/4) | 14.28 (1/7) | 0.427 ($\chi^2$ test) |
| Improvement of penile curvature mean rate percentage/no. patients/total patients | 100 (17/17) | 52.17 (12/23) | 0.002 ($\chi^2$ test) |
| Disappearance of the penile curvature mean rate percentage/no. patients/total patients | 5.88 (1/17) | 0 (0/23) | 0.425 ($\chi^2$ test) |
| Worsening of penile curvature mean rate percentage/no. patients/total patients | 0 (0/17) | 13.04 (3/23) | 0.346 ($\chi^2$ test) |
| Decrease of the penile curvature angle average–degrees + SD | −14.11° ± 8.44 | −7.75 ± 8.72 | 0.031 (ANOVA) |
| Percentage reduction of the penile curvature angle mean rate percentage + SD | −37.75 ± 24.42 | −18.74 ± 18.81 | 0.011 (ANOVA) |
| Restoration of rigid erection mean rate percentage/no. patients/total patients | 80.0 (8/10) | 25.0 (2/8) | 0.536 ($\chi^2$ test) |

effective in treating PD, whereas, lower therapeutic responses were obtained in control group without vitamin E. The significant improvements obtained in group A concern the basic parameters of the disease: plaque size, calcification size, degree of penile curvature and penile rigidity measurement (if erectile dysfunction was present) (see Table 2). Furthermore, our results showed that increase in plaque size occurred only in the group B (17.1%)($p = 0.032$), thus affirming that vitamin E can help to prevent the progression of PD. We think vitamin E is more effective when it is combined with other drugs, but this consideration should be also made to any substance in the medical management of PD. Our findings confirm that the best approach for treating PD is multimodal therapy (Levine, 2003; Lemourt Oliva *et al.*, 2005; Mirone, 2007; Taylor & Levine, 2008; Cortés-González & Glina, 2010; Kuehhas *et al.*, 2011; Abern *et al.*, 2012; Cavallini *et al.*, 2012) because it was able to achieve greater results than each single drug alone. At the end of the treatment (6 months), for each patient we have planned 1 year of conservative treatment, until the stabilization of disease. The proposed treatment consists in the same multimodal therapy of group A, with half doses of medications and with a once-a-month penile injection.

Considering the outcome of our study, the meta-analyses and studies, which consider vitamin E ineffective in treating PD, should not be taken into account because vitamin E was used as monotherapy.

## CONFLICT OF INTEREST STATEMENT

The Authors declare no conflicts of interest.

## AUTHORS' CONTRIBUTIONS

Paulis G.: Initiated, designed and coordinated the study, drafted the manuscript and performed the statistical analysis. Brancato T.: Participated in its design and coordination and helped to draft the manuscript. D'Ascenzo R.: Collected all the diagnostic results and performed the ultrasound examinations. De Giorgio G.: Collected all the diagnostic results and performed the ultrasound examinations. Nupieri P.: Participated in coordination and helped to draft the manuscript. Orsolini G.: Participated in coordination and helped to draft the manuscript. Alvaro R.: Participated in its design and coordination and helped to draft the manuscript. All Authors have given final approval of the version to be published.

## REFERENCES

Abern MR, Larsen S & Levine LA. (2012) Combination of penile traction, intralesional verapamil, and oral therapies for Peyronie's disease. *J Sex Med* 9, 288–295.

Abner EL, Schmitt FA, Mendiondo MS, Marcum JL & Kryscio RJ. (2011) Vitamin E and all-cause mortality: a meta-analysis. *Curr Aging Sci* 4, 158–170.

Bennett NE, Guhring P & Mulhall JP. (2007) Intralesional verapamil prevents the progression of Peyronie's disease. *Urology* 69, 1181–1184.

 

Busse D, Templin S, Mikus G, Schwab M, Hofmann U, Eichelbaum M, Kivistö KT (2006) Cardiovascular effects of (R)- and (S)-verapamil and racemic verapamil in humans: a placebo-controlled study. *Eur J Clin Pharmacol* 62, 613–619.

Cavallini G, Biagiotti G, Koverech A & Vitali G. (2002) Oral propionyl-l-carnitine and intraplaque verapamil in the therapy of advanced and resistant Peyronie's disease. *BJU Int* 89, 895–900.

Cavallini G, Modenini F & Vitali G. (2007) Open preliminary randomized prospective clinical trial of efficacy and safety of three different verapamil dilutions for intraplaque therapy of Peyronie's disease. *Urology* 69, 950–954.

Cavallini G, Biagiotti G & Lo Giudice C. (2012) Association between peyronie's disease and low serum testosterone levels: detection and therapeutic considerations. *J Androl* 33, 381–388.

Chilton CP, Castle WM, Westwood CA & Pryor JP. (1982) Factors associated in the aetiology of peyronie's disease. *Br J Urol* 54, 748–750.

Cortés-González JR & Glina S. (2010) Conservative treatment of Peyronie's disease: colchicine vs. colchicine plus vitamin E. *Actas Urol Esp* 34, 444–449.

Devine CJ Jr, Somers KD, Jordan GH & Schlossberg SM. (1997) Proposal: trauma as the cause of the Peyronie's lesion. *J Urol* 157, 285–290.

Dibenedetti DB, Nguyen D, Zografos L, Ziemiecki R & Zhou XA. (2011) Population-based study of Peyronie's Disease: prevalence and treatment patterns in the United States. *Adv Urol* Vol. 2011, Article ID 282503. Published online 2011 doi: 10.1155/2011/282503. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202120/pdf/AU2011-282503.pdf

Diegelmann RF. (1997) Cellular and biochemical aspects of normal and abnormal wound healing: an overview. *J Urol* 157, 298–302.

Echizen H, Vogelgesang B & Eichelbaum M. (1985) Effects of d,l-verapamil on atrioventricular conduction in relation to its stereoselective first-pass metabolism. *Clin Pharmacol Ther* 38, 71–76.

Gonzalez-Cadavid NF, Magee TR, Ferrini M, Qian A, Vernet D & Rajfer J. (2002) Gene expression in Peyronie's disease. *Int J Impot Res* 14, 361–374.

Ha SK, Moon E & Kim SY. (2010) Chrysin suppresses LPS-stimulated proinflammatory responses by blocking NF-jB and JNK activations in microglia cells. *Neurosci Lett* 485, 143–147.

Hashimoto K, Hisasue S, Kato R, Kobayashi K, Shimizu T & Tsukamoto T. (2006) Outcome analysis for conservative management of Peyronie's disease. *Int J Urol* 13, 244–247.

Hatzimouratidis K, Eardle I, Giuliano F, Hatzichristou D, Moncada I, Salonia A *et al.* (2012) Guidelines on penile curvature. *Eur Urol* [Epub ahead of print], also available in: European Association of Urology (EAU) Guidelines 2012 edition. Available at: http://www.uroweb.org/fileadmin/guidelines/2012_Guidelines_large_text_print_total_file.pdf.

Hauck EW, Diemer T, Schmelz HU & Weidner W. (2006) A critical analysis of nonsurgical treatment of Peyronie's disease. *Eur Urol* 49, 987–997.

Hellstrom WJG. (2009) Medical management of review Peyronie's disease. *J Androl* 30, 397–405.

Jalkut M, Gonzalez-Cadavid N & Rajfer J. (2003) Peyronie's disease: a review. *Rev Urol* 5, 142–148.

Jang Q, Yin X, Lill MA, Danielson ML, Freiser H & Huang J. (2008) Long-chain carboxychromanols, metabolites of vitamin E, are potent inhibitors of cyclooxygenases. *Proc Natl Acad Sci USA* 105, 20464–20469.

Jarow JP & Lowe FC. (1997) Penile trauma: an etiologic factor in Peyronie's disease and erectile dysfunction. *J Urol* 158, 1388–1390.

Karlsen A, Retterstøl L, Laake P, Paur I, Kjølsrud-Bøhn S, Sandvik L *et al.* (2007) Anthocyanins inhibit nuclear factor-kappa B activation in monocytes and reduce plasma concentrations of pro-inflammatory mediators in healthy adults. *J Nutr* 137, 1951–1954.

Kendirci M & Hellstrom WJ. (2004) Critical analysis of surgery for Peyronie's disease. *Curr Opin Urol* 14, 381–388.

Kirsh VA, Hayes RB, Mayne ST, Chatterjee N, Subar AF, Dixon LB *,et al.* PLCO Trial. (2006) Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. *J Natl Cancer Inst* 98, 245–254.

Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ *et al.* (2011) Vitamin E and the risk of prostate cancer: the selenium and Vitamin E cancer prevention trial (SELECT). *JAMA* 306, 1549–1556.

Kuehhas FE, Weibl P, Georgi T, Djakovic N & Herwig R. (2011) Peyronie's Disease: nonsurgical therapy options. *Rev Urol* 13, 139–146.

Kunstmann H. (1954) Treatment of induratio penis plastica with vitamin E. *Medizinische* 23, 125–126.

Lemourt Oliva M, Filgueiras Lopez E, Rodrıguez Barroso A, Gonzalez Oramas E & Bordonado R. (1998) Clinical evaluation of the use of propoleum in Peyronie's disease. *Arch Esp Urol* 51, 171–176.

Lemourt Oliva M, Rodriguez Barroso A, Bordonado Ramirez R, Gonzalez Oramas E & Molina Castillo F. (2003a) Study of propoleum dosage in Peyronie's disease. *Arch Esp Urol* 56, 814–819.

Lemourt Oliva M, Rodriguez Barroso A, Puente Guillen M, Vega Guerrero C, Navarro Cutino M & Perez Monzon A. (2003b) Propoleum and Peyronie's disease. *Arch Esp Urol* 56, 805–813.

Lemourt Oliva M, Fragas Valdes R, Bordonado Ramirez R, Santana JL, Gonzalez Oramas E & Merino A. (2005) Peyronie's disease. Evaluation of 3 therapeutic modalities: propoleum, laser and simultaneous propoleum-laser. *Arch Esp Urol* 58, 931–935.

Levine LA. (2003) Review of current nonsurgical management of Peyronie's disease. *Int J Impot Res* 15(Suppl 5), S113–S120.

Levine LA, Merrick PF & Lee RC. (1994) Intralesional verapamil injection for the treatment of Peyronie's disease. *J Urol* 151, 1522–1524.

Marquez N, Sancho R, Macho A, Calzado MA, Fiebich BL & Munoz E. (2004) Caffeic acid phenethyl ester inhibits T-cell activation by targeting both nuclear factor of activated T-cells and NF-kappaB transcription factors. *J Pharmacol Exp Ther* 308, 993–1001.

Mirone V. (2007) Combination nonsurgical therapy. In: *Peyronie's disease. A Guide to Clinical Management* (ed. L A Levine), pp. 111–119. Humana Press, Totowa, NJ.

Mulhall JP, Creech SD, Boorjian SA, Ghaly S, Kim ED, Moty A *et al.* (2004) Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. *J Urol* 171, 2350–2353.

Natarajan K, Singh S, Burke TR Jr, Grunberger D & Aggarwal BB. (1996) Caffeic acid phenethyl ester is a potent and specific inhibitor of activation of nuclear transcription factor NF-kappa B. *Proc Natl Acad Sci USA* 93, 9090–9095.

Nugteren HM, Nijman JM, de Jong IJ & van Driel MF. (2011) The association between Peyronie's and Dupuytren's disease. *Int J Impot Res* 23, 142–145.

O'Leary KA, de P-TS, Needs PW, Bao YP, O'Brien NM & Williamson G. (2004) Effect of flavonoids and vitamin E on cyclooxygenase-2 (COX-2) transcription. *Mutat Res* 551, 245–254.

Paixão J, Dinis TC & Almeida LM. (2011) Dietary anthocyanins protect endothelial cells against peroxynitrite-induced mitochondrial apoptosis pathway and Bax nuclear translocation: an *in vitro* approach. *Apoptosis* 16, 976–989.

Paulis G & Brancato T. (2012) Inflammatory mechanisms and oxidative stress in Peyronie's disease. Therapeutic "rationale" and related emerging treatment strategies. *Inflamm Allergy Drug Targets* 11, 48–57.

Paulis G, D'Ascenzo R, Nupieri P, De Giorgio G, Orsolini G, Brancato T *et al.* (2012) Effectiveness of antioxidants (propolis, blueberry, vitamin E) associated with verapamil in the medical management of Peyronie's disease: a study of 151 cases. *Int J Androl* 35, 521–527.

Prieto Castro RM, Leva Vallejo ME, Regueiro Lopez JC, Anglada Curado FJ, Alvarez Kindelan J & Requena Tapia MJ. (2003) Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. *BJU Int* 91, 522–524.

 

Pryor JP & Farrell CF. (1983) Controlled clinical trial of vitamin E in Peyronie's disease. *Prog Reprod Biol* 9, 41–45.

Rajasekaran M, Hellstrom WJ & Sikka SC. (2001) Nitric oxide induces oxidative stress and mediates cytotoxicity to human cavernosal cells in culture. *J Androl* 22, 34–39.

Rehman J, Benet A & Melman A. (1998) Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. *Urology* 51, 620–626.

Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J & Mishrs A. (1997) The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 49, 822–830.

Safarinejad MR, Hosseini SY & Kolahi AA. (2007) Comparison of vitamin E and propionyl-L-carnitine, separately or in combination, in patients with early chronic Peyronie's disease: a double-blind, placebo controlled, randomized study. *J Urol* 178, 1398–1403.

Safarinejad MR, Asgari MA, Hosseini SY & Dadkhah F. (2010a) A double-blind placebo-controlled study of the efficacy and safety of pentoxifylline in early chronic Peyronie's disease. *BJU Int* 106, 240–248.

Safarinejad MR. (2010b) Safety and efficacy of coenzyme Q10 supplementation in early chronic Peyronie's disease: a double-blind, placebo-controlled randomized study. *Int J Impot Res* 22, 298–309.

Scardino PL & Scott WW. (1949) The use of tocopherols in the treatment of Peyronie's disease. *Ann New York Acad Sci* 52, 390–393.

Schwarzer U, Sommer F, Klotz T, Braun M, Reifenrath B & Engelmann U. (2001) The prevalence of Peyronie's disease: results of a large survey. *BJU Int* 88, 727–730.

Serraino I, Dugo L, Dugo P, Mondello L, Mazzon E, Dugo G *et al.* (2003) Protective effects of cyanidin-3-O-glucoside from blackberry extract against peroxynitrite-induced endothelial dysfunction and vascular failure. *Life Sci* 73, 1097–1114.

Sikka SC & Hellstrom WJG. (2002) Role of oxidative stress and antioxidants in Peyronie's disease. *Int J Impot Res* 14, 353–360.

Somers KD & Dawson DM. (1997) Fibrin deposition in Peyronie's disease plaque. *J Urol* 157, 311–315.

Song JJ, Cho JG, Hwang SJ, Cho CG, Park SW & Chae SW. (2008) Inhibitory effect of caffeic acid phenethyl ester (CAPE) on LPS-induced inflammation of human middle ear epithelial cells. *Acta Otolaryngol* 128, 1303–1307.

Steinberg CL. (1951) Tocopherols in treatment of primary fibrositis; including Dupuytren's contracture, periarthritis of the shoulders, and Peyronie's disease. *AMA Arch Surg* 63, 824–833.

Taylor FL & Levine LA. (2008) Non-surgical therapy of Peyronie's disease. *Asian J Androl* 10, 79–87.

Trost LW, Gur S & Hellstrom WJ. (2007) Pharmacological management of Peyronie's disease. *Drugs* 67, 527–545.

Van de Water L. (1997) Mechanisms by which fibrin and fibronectin appear in healing wounds: implications for Peyronie's disease. *J Urol* 157, 306–310.

Vanni AJ & Bennett NE. (2009) Current treatment and management of the acute phase of Peyronies's disease. *Arch Esp Urol* 62, 614–622.

Wang Q, Xia M, Liu C, Guo H, Ye Q, Hu Y *et al.* (2008) Cyanidin-3-O-beta-glucoside inhibits iNOS and COX-2 expression by inducing liver X receptor alpha activation in THP-1 macrophages. *Life Sci* 83, 176–184.

Weinstein SJ, Wright ME, Lawson KA, Snyder K, Männistö S, Taylor PR *et al.* (2007) Serum and dietary vitamin E in relation to prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 16, 1253–1259.

Wright ME, Weinstein SJ, Lawson KA, Albanes D, Subar AF, Dixon LB *et al.* (2007) Supplemental and dietary vitamin E intakes and risk of prostate cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev* 16, 1128–1135.

Zargooshi J. (2004) Trauma as the cause of Peyronie's disease: penile fracture as a model of trauma. *J Urol* 172, 186–188.

 