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Treatment of Erectile Dysfunction and Male Infertility with Prelox®

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Abbreviations: cGMP, cyclic guanosine monophosphate; DIR, digital inflection rigiometry; ED, erectile dysfunction; eNOS, endothelial nitric oxide synthase; HDL, high-density lipoprotein; IIEF, International Index of Erectile Function; L-arg asp, L-arginine aspartate; NO, nitric oxide; NOS, nitric oxide synthase; NS, not significant; PSA, prostate specific antigen; SHIM, ‘Sexual Health Inventory for Men’.

Abstract

Prelox® is a trademarked proprietary blend of French maritime pine bark extract, Pycnogenol®, and L-arginine aspartate. This chapter reviews and discusses results of clinical studies carried out with Prelox® for men with erectile dysfunction (ED). A first experimental study tested L-arginine aspartate (dosage 3 g/day) both alone as well as in combination with Pycnogenol® for recovery of ED in 40 men. Application of L-arginine aspartate alone for 1 month was effective in only 5% of men, while the addition of Pycnogenol® (80 mg/day) to the L-arginine aspartate regimen was effective during a second month’s treatment in recovering erectile function in 80% of the cases ($P < 0.01$). An increase of the daily Pycnogenol® dose to 120 mg further increased the number of men with restored sexual function to a remarkable 92.5%.

Another clinical study extended these results by recruiting 50 ageing men with low testosterone levels who simultaneously suffered from ED as well as from subfertility because of impaired sperm motility and morphology. Men were supplemented with Prelox® over a period of 11 months. Again a statistically significant 76% of men experienced restored sexual function. The efficacy was sustained over the whole treatment period and no side effects occurred. Furthermore, Prelox® regimen had improved sperm parameters at the end of the 1-year treatment and 40% of the couples had achieved pregnancy. The improved sperm quality in subfertile men in response to Pycnogenol® supplementation has recently been discovered in US studies.

A third clinical study carried out in the USA applied modern techniques, digital inflection rigidometry (DIR) and the International Index of Erectile Function (IIEF) score, to substantiate the efficacy of Prelox® for 37 men with mild ED. After using Prelox® for 6 weeks, 81.1% of men judged supplementation with Prelox® to be effective and 70.3% showed an increased IIEF score and a generally increased penile rigidity. Also 73% of the men reported easier initiation of erection, 70.3% reported it was easier to sustain the erection and 65% of the men reported to have increased morning erections. Data analysis revealed that Prelox® was particularly effective for milder forms of ED.

In a fourth clinical study involving 20 men with mild forms of ED patients were evaluated with a men’s performance test questionnaire following intake of Prelox® for a period of 6 weeks; 45% of men reported normal erections after treatment. Results showed best improvement for men aged between 30 and 39, a 50% improvement in men between 40 and 60, whereas the two patients over 60 showed no response.

Another investigation included 42 patients with asymptomatic varicoceles and a control group of 23 subjects. Patients were treated with Prelox® or placebo for a period of 3 months. Quality of sperm measured in terms of sperm count, motility and morphology was highly significantly improved in the Prelox® group, no significant changes were noted in the placebo group. Libido and sexual performance was also increased in the Pycnogenol® group.

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All five clinical studies uniformly showed that male sexual function was restored during supplementation with Prelox®. Moreover, there were no side effects in any of the studies and no cases of hyper-stimulation or priapism have been reported. Prelox® is a safe and efficacious long-term regimen for ageing men who wish to compensate for early signs of flawed sexual performance and regain the ability to respond spontaneously to sexual stimulation.

**Keywords**: L-arginine, male idiopathic infertility, Pycnogenol®, sperm parameters.

**Introduction**

**Physiology of erectile function**

Erectile dysfunction (ED) is defined as the inability to attain and/or maintain a penile erection sufficient to complete a satisfactory sexual intercourse (NIH, 1993). With increasing age erectile function deteriorates progressively (Montorsi et al., 2002). The association of ageing and ED was shown in several epidemiological studies. Probably the most comprehensive epidemiological study was the Massachusetts Male Ageing Study, which surveyed health and ageing of more than 1000 men including a questionnaire on sexual function and activity (Feldman et al., 1994). From their data followed a clear correlation linking increasing age with a lower probability of getting normal erections. The probability for complete ED increases from about 5% at the age of 50 to more than 30% of the age of 70.

During arousal, the ageing man presents a lengthening of the excitement phase with a delayed erection, a lengthening of the plateau phase with a longer interval to ejaculation and decreased penile rigidity. During orgasm, a shorter ejaculation event with an increased incidence of resolution without ejaculation is common (Wespes, 2002).

Penile erection is a vascular dynamic phenomenon under psychological control. The sexual stimulus travels through the spinal cord to reach the corpora cavernosa. The terminal branches of the cavernous nerves release several neurotransmitters, the most important ones being nitric oxide (NO), acetylcholine and prostaglandins. These erectogenic neurotransmitters act in concert with vasodilators of the endothelium, predominantly NO. Increased blood flow through the penile arteries stimulates the endothelium leading to further increase of NO (Simonsen et al., 2002). NO diffuses to the smooth muscle layers to stimulate guanylyl cyclase, followed by intracellular increase of cyclic guanosine monophosphate (cGMP) as second messenger, which subsequently triggers muscle relaxation. Ultimately, these processes allow enhanced inflow of blood into penile arteries and sinusoids, restriction of venous outflow and entrapment of pressurized blood in the corpora cavernosa.

With normal ageing physiological changes occur in male sexual activity, impairing erectile function. These changes largely comprise endocrinological (hormonal) and vascular abnormalities (Montorsi et al., 2002). Alterations in blood flow to and from the penis are thought to be the most frequent cause of male ED (Simonsen et al., 2002). Many alterations of penile arterial endothelial cell function relate to arterial risk factors such as atherosclerosis and hypertension, which occur more frequently at higher age. A general age-related decline of endothelial function affects bioactivity and availability of NO (Carr and Frei, 2000). Thus, promising strategies to counteract impaired erectile function at higher age address the supply with NO or prolong the bioactivity of NO’s second messenger cGMP.

**Composition and pharmacology of Prelox®**

Prelox® is a branded, unique preparation of French maritime pine bark extract, Pycnogenol®, and L-arginine aspartate, exclusively distributed worldwide by Horphag Research Ltd, UK.

Pycnogenol® consists of polyphenols, it contains phenolic acids (p-hydroxy benzoic, protocatechuic, vanillic, gallic, p-cumaric, caffeic and ferulic acid) and taxifolin and catechin. The main constituents of Pycnogenol® are procyanidins: biopolymers of catechin or epicatechin units with a chain length of up to dodecamers (Rohdewald, 2002).

A central function of Pycnogenol® is its ability to enhance endothelial production of NO from the substrate L-arginine by the endothelial nitric oxide synthase (eNOS). A pharmacological study has shown that Pycnogenol® dose-dependently increases the diameter of an adrenaline-constricted arterial blood vessel (Fitzpatrick et al., 1998). Pycnogenol® did not relax the artery in the absence of endothelial cells or when nitric oxide synthase (NOS) was inhibited by N-methyl-L-arginine, an ineffective substrate for NOS. However, when the natural substrate L-arginine was added, relaxation was restored. Unlike other antioxidants Pycnogenol® apparently does not act by merely extending the half-life of NO by preventing its oxidation to inactive peroxynitrite by superoxide (Carr and Frei, 2000). Vasorelaxant activity of Pycnogenol® remained unaltered when peroxynitrite development was inhibited by the presence of superoxide dismutase. These findings led to the proposition that Pycnogenol® stimulates production of NO from L-arginine by eNOS (Rohdewald, 2005) by enhancing synthesis of this enzyme.

L-arginine is the precursor of NO and its abundant availability is understood to support more efficient NO production. Indeed, pharmacologic studies with adult and aged male rats showed that oral supplementation with high doses of L-arginine statistically significantly increased maximal intracavernosal pressure and penile eNOS activity was increased by almost 100% (Moody et al., 1997). It was
postulated that L-arginine in the penis may be a substrate-limiting factor for eNOS activity.

As Pycnogenol® was found to stimulate eNOS to more efficiently produce NO, a more abundant L-arginine as precursor will further enhance activity. In Prelox®, L-arginine is combined with Pycnogenol® as L-arginine aspartate. The ionized arginine is easily water-soluble and thus facilitates better absorption. L-aspartate plays a crucial role in the Krebs cycle (citrate cycle), the central biochemical cellular pathway for gaining energy and metabolite biosynthesis. Indeed, supplementation of rats with L-aspartate was shown to enhance physical performance (Lancha et al., 1995). This function for Prelox® is not intentional, yet might prove to be beneficial for certain individuals.

Clinical Studies with Prelox®

Discovery of Prelox® for improvement of erectile function

At the Medical University of Sofia (Bulgaria) Dr Stanislavov’s group tested natural remedies for treatment of men with impaired erectile function (Stasialov and Nikolova, 2003). Forty men participated in this study, aged between 25 and 45 years (mean age 36.6 ± 5.3 years), suffering from an inability to achieve and sustain an adequate erection sufficient for successful intercourse. Men with organic causes for ED were excluded from the study. The erectile function before and after treatment was assessed using the questionnaire according to O’Leary (O’Leary et al., 1995). The O’Leary questionnaire was complemented by additional questions to assess the ratio of successful to unsuccessful attempts of erections for intercourse. Specific questions were raised regarding the nature of unsuccessful intercourse: too weak penile rigidity, delayed development of a sufficient erection, or erection was not sustained long enough. During the first 3 weeks’ run-in phase subjects did not receive medication to obtain reliable baseline values.

In a first treatment approach men received three portions of 1 g L-arginine aspartate (dissolved in 5 ml water in ampoules)/day over a period of 1 month. As a result two men (5% of patients) experienced normal erections (Fig. 86.1). During the following month subjects continued taking the same dosage of L-arginine aspartate plus 40 mg Pycnogenol® twice a day. This led to a dramatic and statistical significant recovery of normal erectile function in 32 men (80% of patients). This successful result was the first discovery of a unique combination of Pycnogenol® with L-arginine aspartate, denominated Prelox®.

The efficacy of the L-arginine aspartate–Pycnogenol® combination, Prelox®, was further established by increasing the daily dosage of Pycnogenol® to 120 mg a day during the next month’s treatment. The number of men with restored normal erectile function was further increased to 37, equivalent to 92.5% of all subjects (Fig. 86.1).

In those patients who gained normal erectile function during treatment, Stanislavov and Nikolova estimated the time necessary to initiate penile erection as well as the period of time it sustained (Table 86.1). The two patients responding to L-arginine aspartate treatment required 10 min to achieve an erection. Again, the combination of L-arginine aspartate with Pycnogenol®, Prelox®, dramatically reduced the time for development of an erection. More importantly, the duration of the erection was prolonged. An increase of Pycnogenol® dose further improved these parameters.

The authors of the study reported that Prelox® was effective irrespective of the age of subjects, however, no men

### Fig. 86.1. Restoration of normal erections of men with mild forms of erectile dysfunction (ED). While supplementation with L-arginine aspartate (L-arg asp) (3 g/day) only gave little effect, the combination of L-arg asp with 80 mg Pycnogenol®/day (= Prelox®) gave a statistically significant increase (*) of men with restored erectile function. An increase of the Pycnogenol® dose further increased the benefit (Source: Stanislavov and Nikolova, 2003).

### Table 86.1. Erectile response of patients who experienced restored erectile function to spontaneous sexual stimulation (Source: Stanislavov and Nikolova, 2003).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>L-arg asp* (3 g/day) for 1 month</th>
<th>L-arg asp (3 g/day) + Pycnogenol® (80 mg/day) for 2 months</th>
<th>L-arg asp (3 g/day) + Pycnogenol® (120 mg/day) for 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time (min) until response emerges</td>
<td>–</td>
<td>10 ± 2</td>
<td>4 ± 1</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Mean time (min) of duration of erection</td>
<td>–</td>
<td>2 ± 1</td>
<td>4 ± 1</td>
<td>15 ± 3</td>
</tr>
</tbody>
</table>

*L-arg asp, L-arginine aspartate.*
older than 45 years participated on the study. No side effects or signs of hyper-stimulation or priapism were observed.

**Long-term Prelox® regimen**

The research group in Sofia, headed by Stanislavov, extended their Prelox® research programme to men with abnormally low testosterone levels, suffering from ED but who had additional fertility problems (Stanislavov and Nikolova, 2005). Fifty ageing men (> 45 years) with diagnosed subfertile characteristics were enrolled for this study.

Inclusion criteria were testosterone levels below normal (below 12 mg/ml), symptoms of ED and complaints about secondary infertility.

Exclusion criteria were severe cardiovascular diseases, hypertension, renal failure, hepatic insufficiency, endocrine abnormalities and psychiatric disorders. Patients also were excluded if they were currently or had recently been treated for ED with vasoactive medications, surgery or any mechanical device. Concomitant use of other therapies for ED was not allowed.

Sexual response rates were derived from a global efficacy questionnaire, summarizing observations from the patient’s diaries for erectile function.

All patients were undergoing a detailed seminological investigation before and after treatment consisting of the following tests: volume of ejaculate, sperm density and motility, percentage of morphologically normal sperm, movement characteristics of sperm and penetration depth in cervical mucus.

Sperm were also tested for eNOS activity before and after treatment using a radial enzyme diffusion method, detecting the conversion of L-arginine into citruline.

Western blots were performed to identify isoforms of NOS with antibodies obtained from Affinity Research Products Ltd UK using the method of Roberts (1986).

Blood samples were taken before and after treatment for analysis with enzymatic standard methods for levels of total cholesterol, high-density lipoprotein (HDL), triglycerides, prostate specific antigen (PSA) and glucose.

Patients received the following daily treatment: Pycnogenol® three × 40 mg tablets (Hankintatukku, Finland), three × one ampoule L-arginine aspartate 1 g, equivalent to 0.57 g L-arginine (Sargenor, Sarget Pharma, Cedex, France), together with meals. Testosterone undecanoate (Andriol®) was given as 40 mg tablets, one tablet in the morning and two tablets in the evening, to mimic the circadian rhythm.

Supplementation started with 1.71 g L-arginine/day for the first month, thereafter treatment was continued with L-arginine plus Pycnogenol® (now marketed as Prelox®) and testosterone undecanoate over a period of 11 months, so that total treatment period of patients was 12 months.

The questionnaire for establishing the patients’ ability for obtaining and maintaining a successful erection was completed by all participants. Before treatment only 10% of the patients reported normal erections (Table 86.2). After 1 month of treatment with L-arginine aspartate alone this percentage increased insignificantly to 16%. The percentage of men with normal erections increased to 76% at the end of the treatment period with Prelox® and testosterone undecanoate.

However, the improvement of erectile function had to be paralleled by improvement of seminological parameters to achieve successful effects on patient’s fertility. Seminal parameters improved highly significantly after the treatment period of 12 months (Table 86.3). Sperm quality improved in terms of a higher percentage of morphologically normal sperm, the volume of ejaculate was increased more than four fold, and the total count (in millions per ejaculate) and sperm motility were significantly enhanced.

The more detailed investigation of those men with normal morphology of sperm demonstrated dramatic improvements of characteristics of spermatozoa motility, leading finally to better spermatozoal penetration into ovulatory cervical mucus. Penetration into cervical mucus was increased by a factor of two, corresponding to the doubling of spermatozoa velocity after treatment. Also the content of lytic enzymes in sperm was increased.

Table 86.2. Percentage and number of patients with normal erections following treatment with Prelox® and Andriol® (Source: Stanislavov and Nikolova, 2005).

<table>
<thead>
<tr>
<th>Erection</th>
<th>Before treatment</th>
<th>After 1 month treatment with L-arginine (only)</th>
<th>After 3 months treatment with Prelox® + testosterone propionate</th>
<th>After 6 months treatment with Prelox® + testosterone propionate</th>
<th>After 12 months treatment with Prelox® + testosterone propionate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10% (5)</td>
<td>16% (8) NS</td>
<td>40% (20)*</td>
<td>58% (29)*</td>
<td>76% (38)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Statistically significant difference to start: NS, not significant; *, &gt; 0.05; **, &gt; 0.01.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 86.3. Seminal parameters before and after combination treatment of 50 ageing males (Source: Stanislavov and Nikolova, 2005).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before 11 months combined therapy</th>
<th>After 11 months combined therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejaculate volume (ml)</td>
<td>0.7 ± 0–3</td>
<td>3.0 ± 1.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Sperm density (10⁶/ml)</td>
<td>52 ± 18</td>
<td>85 ± 22</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Sperm motility (%)</td>
<td>41 ± 12</td>
<td>65 ± 11</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Morphologically normal spermatozoa (%)</td>
<td>45 ± 8</td>
<td>61 ± 9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>pH</td>
<td>7.4 ± 0.2</td>
<td>7.3 ± 0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>
the exclusive presence of the endothelial form of NOS, while neither inducible NOS nor neuronal NOS were found.

The eNOS activity, demonstrated semi-quantitatively in our microradial enzyme diffusion system, increased clearly during treatment with Prelox® and testosterone undecanoate (Fig. 86.2). Interestingly, specimens from patients with diabetes mellitus, hypertension or hyperlipidaemia showed very little eNOS activity, and the eNOS concentration in sperm from an aged male (56 years) was considerably lower compared to a potent male.

The investigation of blood clinical chemistry revealed positive changes in lipid parameters after treatment, including significantly lower values of cholesterol and triglycerides and a significant increase of HDL. Values for PSA and glucose were not significantly affected (Table 86.4).

During treatment no unfavourable side effects were observed. The most important result from the viewpoint of the 50 patients is that 22 achieved fertilization during the 11 month treatment period.

The positive influence of the supplementation with Prelox® and Andriol® on erectile function was to be expected according to results showing a restoration of erectile function after treatment with Prelox® (Stanislavov and Nikolova, 2005). However, in this group of patients with low testosterone levels only 76% could gain normal erection following treatment for 11 months with the combination, whereas in the group of younger men (mean age 37 years) with normal testosterone levels 2 months of supplementation were sufficient for a success rate of 92.5% (Stanislavov and Nikolova, 2003). Consequently, the treatment period for men of higher age and low testosterone levels has to be extended.

Comparison of our results with the findings of Roseff (2002), who found only a modest improvement in the quality of sperm after treatment of subfertile men with 200 mg Pycnogenol® for 90 days, points to a greater benefit of supplementation with Prelox® and testosterone. Although Roseff observed a significant improvement of capacitated sperm morphology and an increase in a mannose-binding assay, he could not demonstrate a significant improvement of sperm motility and sperm density. One can conclude from that comparison that the main cause for our more favourable results is the simultaneous administration of L-arginine and Pycnogenol® (Prelox®), so that the eNOS activity is stimulated and provides an extensive amount of substrate for NO production, which in turn positively affects seminal parameters.

Western blot analysis proves the presence of eNOS in human sperm. It could be shown for the first time that supplementation of patients with a combination of Prelox® and Andriol® increased clearly the quantity of eNOS in sperm.

With progressing time of treatment, the concentration of eNOS increased regularly. Furthermore, the enzyme-diffusion test demonstrated that pathological conditions lead to subnormal activity of eNOS in patients with damaged endothelial function such as diabetes or hypertension.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.82 ± 1.06</td>
<td>4.93 ± 0.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>0.94 ± 0.21</td>
<td>1.29 ± 0.29</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.86 ± 0.54</td>
<td>1.25 ± 0.60</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PSA (mmol/l)</td>
<td>2.9 ± 0.4</td>
<td>3.1 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose fasting (mmol/l)</td>
<td>5.2 ± 0.6</td>
<td>5.4 ± 0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fig. 86.2. Spermatozoa NOS activity during treatment with Prelox® and testosterone propionate (Andriol®) in (a): 1 – before treatment; 2 – after 1 months’ treatment; 3 – after 3 months’ treatment; 4 – after 6 months’ treatment; 5 – after 12 months’ treatment. (b) Specimens of untreated patients with different diagnoses: 1 – diabetes mellitus; 2 – hypertension; 3 – normal potent male; 4 – elder male (56); 5 – hyperlipidaemia.
These experiments underline that the prominent physiological role of the NO-cGMP pathway in the genital tract affects not only the functions of the smooth musculature of the human genito-urinary tract or the seminal vesicles (Ückert et al., 2003) but also the function of spermatozoa.

The stimulation of eNOS after treatment with the combination of Prelox® and Andriol® is most probably based on the action of Pycnogenol®.

Pycnogenol® stimulates NO production via stimulation of eNOS in the aortic endothelium in vitro (Fitzpatrick et al., 1998). The clear increase of eNOS in sperm during the treatment period confirms the previous in vitro findings.

Intake of Pycnogenol® elevated levels of NO and prostacyclin, while concentrations of endothelin-1 declined in patients with hypertension (Liu et al., 2004a), as well as with diabetes mellitus (Liu et al., 2004b). These results demonstrate a recovery of impaired endothelial function by supplementation with Pycnogenol®. We speculate that restoration of sperm function is related at least in part to the increase in eNOS activity, strengthened by simultaneous supply with NO precursor L-arginine.

Another contributing factor is most probably the excellent antioxidative activity of Pycnogenol®. Pycnogenol® supplementation significantly enhanced the antioxidative capacity of blood of volunteers (Devaraj et al., 2002). The scavenging of free radicals by Pycnogenol® may protect the sensitive sperm against oxidative stress, which are particularly vulnerable to peroxidation (Alvarez et al., 1987; Kim and Parthasarathy, 1998). Positive effects of antioxidant therapy on in vitro fertilization rates underline the importance of antioxidative supplements for sperm function (Geva et al., 1996).

The lower values of total cholesterol and triglycerides and enhanced HDL levels after treatment may contribute to an improved sexual wellness as an impaired lipid metabolism has a negative impact on endothelial and sexual function.

The clinical relevance of improved erectile function as well as of improved sperm quantity and quality is confirmed by the fact that 44% of patients achieved pregnancy.

Finally, the intensified sexual wellness had a great impact on the psychological condition of the participants. They stated that treatment had improved their ability to engage in sexual activity. The additional questions at the end of the trial demonstrated a statistically significant improvement of eNOS activity, strengthened by simultaneous supply with NO precursor L-arginine.

According to the experience of Dr Stanislavov, substitution of low testosterone levels with testosterone propionate alone did not improve sexual function and sperm quality in clinical practice to the same remarkable extent as that observed in treatment combined with Prelox®.

American Prelox® study

Lamm and Couzens (2003) evaluated the efficacy of Prelox® for improving mild forms of ED. The widely accepted International Index of Erectile Function (IIEF) questionnaire was used for evaluation of men’s erectile performance, which yields scores between 0 and 75 (Rosen et al., 1997). Furthermore, with digital inflection rigidometry (DIR) using the instrument DIR H501 (UROAN21, Palma de Mallorca, Spain) the axial penile rigidity in grams was measured as an objective parameter for the efficacy of Prelox®.

Initially, 40 men were enrolled for the trial of which three, however, did not return for the second visit. The age range of the 37 men who completed the trial was: 30–39 years (eight), 40–49 years (14), 50–59 years (14), over 60 years (one).

Men with milder forms of ED were selected using the ‘Sexual Health Inventory for Men’ (SHIM) questionnaire. The SHIM includes only five of the IIEF questions and is easier and faster to use at the recruitment level. The SHIM score ranges between 0 and 25. A value lower than 22 indicates abnormal erectile function. Men with SHIM between 22 and 11 were selected, thus excluding men with more pronounced ED. The mean baseline SHIM score of men who completed the trial was 18.05 ± 2.49. At baseline, subjects had to complete the IIEF score and were provided a DIR H501 to measure their penile rigidity during sexual arousal at home. They were instructed to take four Prelox® tablets/day, each tablet containing 20 mg Pycnogenol® and 750 mg L-arginine aspartate, over a period of 6 weeks. Finally, they completed the IIEF questionnaire and measured penile rigidity again. Together with the second IIEF questionnaire seven questions were added referring to the overall sexual satisfaction. These additional questions were: Since taking the pills,

- …have you had an increase in morning erections?
- …have you had an increase in sexual fantasies?
- …has it been easier to initiate erections?
- …has it been easier to sustain an erection?
- …has your partner noted any change in your sexual interest?
- …has your partner noted any change in your sexual performance?

The outcome of the study was a total of 30 men (81.1%) stating that treatment had improved their ability to engage in sexual activity. The additional questions at the end of the trial demonstrated a statistically significant improvement of erectile function: 73% of the subjects reported that Prelox® supplementation made it easier to initiate an erection, and 70.3% stated that Prelox® made it easier to sustain an erection.

Patients reported an increase of morning erections, sexual dreams and fantasies. Partners noted higher sexual interest and performance.

The DIR readings reflected the improvement, showing higher penile rigidity values. However, during sexual excitement the penile rigidity varied considerably from one reading to another within the time frame of minutes, so values could not be evaluated for statistical analysis.

A closer examination of the data showed that Prelox® was particularly effective for those men with milder forms of ED. Classification of men into three groups according to their ED severity, as taken from SHIM scores at baseline, reveals an increased efficacy of Prelox® particularly for moderate and milder ED. No side effects were reported, all men tolerated Prelox® very well.
**Improvement of erectile function and sperm quality in patients with varicocele and low fertility**

Varicocele is the most frequent correctable cause of male infertility. Among the various available methods, surgery has been demonstrated to have the highest level of efficacy. However, because of the positive reports on Pycnogenol®'s success in improving quality of sperm (Roseff, 2002) and in restoring erectile function (Stanislavov and Nikolova, 2003, 2005) a clinical trial was performed with 65 patients awaiting surgery because of diagnosed asymptomatic varicocele. In the trial 42 patients were treated with four tablets Prelox®/day for 3 months, and a control group of 23 patients received no medication.

All patients were included in the trial after diagnosis by ultrasound for high-reflux varicoceles and full seminal analysis (volume, total number, morphology, motility). Patients evaluated libido and sexual performance by using diaries. Sperm analysis was repeated after 6 months of treatment.

Pycnogenol® stimulates production of NO and prostacyclin and inhibits endothelin-1 formation, so it is able to shift the balance to less vasoconstriction (Liu et al., 2004a, b, c). In addition, Pycnogenol® influences vascular health by improving microcirculation (Belcaro et al., 2005). These effects suggest the use Pycnogenol® as a new natural option to manage asymptomatic varicoceles in a conservative way to improve male fertility.

The 34 patients in the treatment group who completed the trial reported a significant increase of libido and sexual performance after the 3 months’ treatment period. Patients from the control group reported no improvement.

Regarding the fertility status, sperm count was improved in 28 of the 34 patients; 22 subjects had a normal count. Sperm motility increased in 28 of 34 patients; normal values for motility were seen in 21 patients versus only in five patients at enrolment. At inclusion, only six patients had a normal morphology of sperm. Following treatment, morphology was normal in 20 patients and improved in seven other patients. The improvements of sperm quality were clearly significant ($P < 0.001$).

Treatment success in the case of varicoceles with high reflux, affecting both erectile function and quality of sperm, underline the beneficial effects of Pycnogenol® for endothelial function. Proper endothelial function is essential for vascular health by balancing vasoconstriction – caused by endothelin-1 – and vasodilatation – caused by NO and prostacyclin.

**Clinical study with Prelox® in Thailand**

O. Bulpakdi and A. Manoj (unpublished) tested Prelox® on 20 patients between 30 and 60 years for a period of 2 months. Patients were recruited using the Men’s Performance Test Questionnaire, with the following questions:

1. How do you rate your confidence that you could get and keep an erection?
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?
4. When you attempted sexual intercourse, how often was it satisfactory for you?
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Questions 1–4 of the questionnaire were scored from ‘Almost never or never’, worth 1 point, to ‘Almost always or always’, worth 5 points. Response options and scores for the last question were as follows: 0 = ‘Did not attempt intercourse’; 1 = ‘Extremely difficult’; 2 = ‘Very difficult’; 3 = ‘Difficult’; 4 = ‘Slightly difficult’; 5 = ‘Not difficult’. The 20 patients were classified into four groups according to the classification of ED based on the sum of scores: severe ED, 5–10; moderate ED, 11–15; mild ED, 16–20; normal ED, 21–25.

At enrolment, 60% of patients were classified as suffering from mild ED, 30% moderate and 10% as severe ED.

Patients were treated with four Prelox® tablets/day for the first month and two Prelox® tablets daily for the second month.

Patients with severe diseases such as diabetes mellitus, severe hypertension or hypercholesterinaemia were excluded from the study.

After the 2 months’ trial period, 45% of men regained normal erections, 30% fell into the category of mild ED and 15% of moderate ED. The 10% of patients with severe ED remained unchanged.

The best responses were found in the group of men between 30–39 years with mild ED. After treatment, seven of the eight reported normal ED. In the group 40–49 years, the two patients with moderate ED changed to mild ED, and from the four patients with mild ED two turned into normal. Three patients from the 50–59 years age group remained unchanged as moderate ED, only one was improved to mild ED.

The two patients over 60 with severe ED reported no influence of treatment.

The mean of scores over all patients changed significantly from 15.5 before, to 18.5 after treatment ($P > 0.001$).

The trial shows that treatment success is dependent on the stage of ED and age of the patient: the more severe the ED and the older the patient, the less was the success of treatment.

Patients reported no unwanted side effects during treatment.

**Conclusion**

The combination of L-arginine and Pycnogenol®, marketed as Prelox®, has demonstrated in several clinical trials its efficacy in treating ED and, simultaneously, in improving quality of sperm. These findings advocate the use of Prelox® as a safe, natural product to increase male performance, especially for middle-aged men with mild ED.

As a second option Prelox® should be highly recommended in cases of male infertility caused by varicoceles and by poor quality of sperm.
The mechanism of action of Prelox®, stimulating the eNOS and simultaneously supplying an abundant quantity of L-arginine, the substrate for the eNOS, is a way to increase general endothelial health, thus not only improving erectile function and quality of sperm but also reinforcing vascular health and microcirculation.

References


Prelox® and erectile function


