

## **AndroTherm application for “La Peyronie” disease**

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Peyronie’s disease is characterized by a scarring fibrosis within the tunica albuginea of the penis that could lead to penile length loss, narrowing, curvature, erectile dysfunction, pain with erection.

## *Prevalence*

La Peyronie disease ( Induratio penis plastic ), is a developmental condition with acquired fibrotic changes and development of a fibrous plaque (fibrous inelastic scar) on the tunica albuginea of the penis. The Peyronie disease is mostly observable at the men of their middle ages ( 50-60 years ) in Caucasian race (1). The prevalence, commonly reported, is about 3-9% (2), but according to the autopsy statistics the disease would be present in more than 20% of men (3). It can also be an asymptomatic finding in almost 4% of male population seeking medical attention (4, 5). In general the men, 40-60 aged, are affected by Peyronie’s disease in 2-3% (6). We think in fact that shame, fear and poor possibilities of healing (WEBSITE) are the main causes of reduced demand for medical consultation, although it also causes unpleasant side effects such as not agree to the modifications of the penis, reduction of self-esteem, impaired job performances, increased interpersonal conflicts and depression. Now, thanks to the many sources of information, the patient is aware of the limited possibilities of therapy and knows perfectly well that there is little chance of spontaneous recovery (15% of second Mulhall) (7).

## *Pathophysiology*

Relatively little is known about the source of the disease, but nowadays is growing consensus on the possibility of an external stress received, most likely in the erect state, during sexual intercourse or masturbation. Trauma during sexual activity can occur for several reasons: vehement and prolonged masturbation, instinctive and sudden movement of the penis, accidental contrast of the penis against the female perineum, difficulty in penetration due to lack of lubrication of the vagina, lack of penile erection. The abrupt penis deformation during sexual intercourse may disrupt small vessels within the tunica albuginea with blood trapping between layers of the tunica. The hematoma is responsible for excessive release of cytokines, of Transforming Growth Factor (TGF beta1), as a reaction to an autoimmune response. It follows an overproduction of collagen, high production of extracellular matrix, accumulation of fibroblasts and myofibroblasts and decrease of elastic fibers (8). This process, characterized by an abnormal healing of hematoma with production of scar, implies the coexistence of an autoimmune process probably leading to a genetic factor. In 75% of patients affected by Peyronie's disease were shown high levels of antielastin antibodies (9) and a higher incidence of histocompatibility antigens HLA-27 (10). The autoimmune reaction may have, in some individuals, a certain degree of genetic predisposition. Some searches have demonstrated in fact, on cultured cells derived from plaques from Peyronie's disease, chromosomal abnormality, during metaphase, in which the chromosome Y seems the more involved. The actual trauma could lead to inflammation Bleeding and releasing of a number of chemicals that lead to inflammation (12). The closed , layered structure of the tunica may limit the ability to drain the produced inflammatory mediators away from the site of injury, leading to prolonged inflammation ( when the inflammation became chronic it could block the healing process ) (13,14). Nowadays no effective therapy exists for this disease, although there are continuous and ever new attempts. There are many non-surgical treatments for Peyronie’s disease like Vitamin E, Carnitine, Colchicine, Pentoxifylline, and various herbal and complementary remedies like Acetyl-L-Carnitine (ALC) and Dymethyl Sulfoxide (DMSO), or the “ Tracker formula “; enzymes like Wobenzym, Fibrozym, Vitalzym, and Neprinol; as well as the minimally invasive ( local in-situ injection ) treatments of Verapamil, Interferon, Collagenase, and various steroids ( e.g. Glucocorticoids ) could be applied. All of the treatments applied have no or poor efficacy. There are various surgical options to solve this problem (15).

There are huge interest to treat this disease worldwide (16) and also comprehensive books published in the topic (17,18). The transdermal electrophoresis (19) could be effective for the treatment combined with definite drug-therapy called“ trasdermal electromotive drug-therapy“ (EMDTA) (20). This placebo controlled, double-blind study used Orgotein (8mg), Dexamathasone (8mg), Lydocain (120mg) for 20 min three times a week in three weeks duration. The plaque reduction was 79%, the curvature improvement 62% and the pain reduction 100%. Others had also used EMDA with Dexamethasone+Verapamil

combination (21), also compared to Lidocain effect alone (22). EMDA application with Verapamil alone (23) also was effective.

Contrary the new review of non-surgical solutions to treat Peyronie's disease (24), hyperthermia also was applied with success for Peyronie's disease (25). They studied 60 Patients with Peyronie's disease, having a comparison between application of Verapamil and Hyperthermia. The chosen cohort groups were identical in their main relevant parameters (see Figure 1.). Hyperthermia was applied for 20 minutes, twice a week for 5 weeks. A 2nd cycle was made after a 1 month having 10 treatments. The control group received 10mg injection of Verapamil once a week for 3 months. The Verapamil group had no real benefit of the treatment (see Figure 2.). It was significant relief of both subjective and objective symptoms in Hyperthermia treated group, without any adverse side effects (see Figure 3.). The penil curvature decreased by 55,9% with Hyperthermia, while only 3,8% with Verapamil, and the plaque size decreased 42,1% and 2,2% with Hyperthermia and Verapamil, respectively. Similar controlled clinical study is in progress to repeat the results (26). The clinical trial compares the only heat treatment and the treatment group is receiving a combination of Vitamin D and Testosterone injections additional to heat by infrared heating. Learning the failures of many applied conventional treatments and seeing the possible applicability of the heat and the electric field based on current knowledge of the pathophysiological mechanisms involved in the formation of plaque, we developed a new device for treatment of the penis disorders, including Peyronie's disease.

The collected evidences based research data indicate inflammation processes, like the "primum movens" of the cascade process of healing that includes the inflow of platelets, macrophages and mastcells. It has subsequently the release of numerous substances: interleukin, tubular necrosis factor (TNF  $\alpha$ ), platelet-derived growth factor (PDGF), transforming growth factor (TGF  $\beta$ ), which trigger the scarring process by means of the proliferation of fibroblasts, differentiation of myofibroblasts, the deposition of collagen tissue and the transformation of "stem cells" of the tunica albuginea in osteoblasts (27, 28). On this basis the Peyronie's disease plaque is more similar to keloids than to scars. About the formation of keloids is important to note that at the wound site there is a production of heat shock proteins in response to an inflammatory process in order to modulate the intensity of inflammation and the synthetic responses to stress toward the healing of the wound. Overexpression of HSPs can, however, lead to an increase in the inflammatory process and an uncontrolled synthesis process. In some cases, genetic factors, individual predisposition, and physical factors (a particularly aggressive inflammatory process) can play an important role in the formation of keloids. It was reported a high expression of HSPs 27, 47 and 70 within the keloid tissue compared to healthy tissue, which induces both an exaggerated proliferative effect (HSPs 70) and production of matrix (HSP 27.47). (29). In Peyronie's disease has been noted up-regulated expression of certain proteins such as the 'alpha-actin, beta-catenin, and Heat shock proteins (Hsp47), which are established components of fibrosis and wound healing (30).

It is a benign tumor (31), in which:

- 1) Plaque fibroblasts are immortalized cells.
- 2) Plaques and normal tunica albuginea have chromosomal differences.
- 3) Induced immune response by the plaque fibroblasts and their products.
- 4) Mitochondrial dysfunction is observed in plaque fibroblasts.

In coherence of the above conditions it is not a surprise that apoptotic processes can play definite role in plaque formation and its elimination. There is a finding that apoptosis activation (32) albuginea plaques occurs. This, at least, in part is realized via extrinsic pathway (33). Peyronie's disease is known to be associated with Dupuytren's disease (34). Main characteristic of the Dupuytren's disease is palmar aponeurosis hyperplasy and contraction which leads to finger flexion contracture (35). Peyronie's and Dupuytren's diseases have common pathophysiology (36). The imbalance between proliferation and apoptosis, producing malignant growth was thus confirmed for fibrosarcoma, but not the same form for Dupuytren's disease, (37), because this is benign as well, similar to Peyronie's. However both can be regarded as system disease, (38), because the immune system is involved. It was hypothesized that periostin, secreted by Dupuytren's disease cord myofibroblasts into the extra-cellular matrix, promote the transition of resident fibroblasts in the palmar fascia toward a myofibroblast phenotype, thereby promoting disease progression (39).

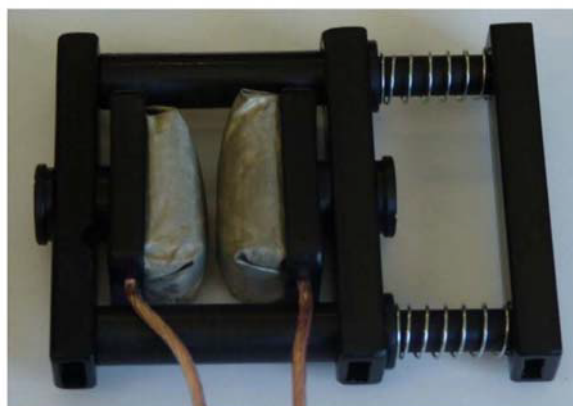
## Method

The traditional hyperthermia had good benefit in treatments of Peyronie's disease, however it is controlled the only single thermodynamic intensive parameter, with the temperature. Oncothermia is a special hyperthermia (40), working on the action of the modulated electric field in the locally treated lesion. It has long experience in the oncology (41). Its idea to use the benefit of electric field makes feasible applying it for Peyronie's disease, unifying the effects of EMDA and heat in a specialize treatment. Our objective is to perform a pilot study with application of a special ( adaptively modified ) kind of oncothermia for Peyronie's disease, called androthermia. The metod is based on the paradigm of the energy-dose control, replacing the single temperature concept (42, 43, 44). With this approach the oncothermia returned to the gold standards of the dose concepts in medicine: instead of the parameter, which can not regarded as dose ( the temperature does not depend on the volume or mass ), Oncothermia uses the energy (  $\text{Kj/Kg}=\text{Gy}$  ), like the radiation oncology uses the same (  $\text{Gy}$  ) to characterize the dosing of the treatment. The requested job is to change the structure of the target, for what a definite energy dose is necessary (45). The historical energy-dose-like control (temperature multiplied by its application time) is physically incorrect, and operates with an overall energy average in the area, instead of a directed and well measurable energy-dose ( measured in  $\text{Kj}$  ). So these points are realized, and called this procedure modulated electro-hyperthermia or oncothermia (46) and specialized now for andrology. The presently applied radiative hyperthermia device, operating on order of magnitudes higher frequency than oncothermia, are in fact capacitive-coupled, because the applicators are definitely in the near-field arrangements. It is a well designed capacitive coupling on 13,56 MHz free-frequency ( 47 ). The process is controlled by the changes of the impedance, and by the absorbed energy, which both are accurately measured. Androtherm device, is the product of Oncotherm GmbH, Troisdorf, Germany (see Figure 1.).



**Figure 1.** Androtherm device (Treat-therm trade-mark)

It was developed for Peyronie's disease, concentrating the plaque dissolution, using all the experiences and achievements from the past 20 years. A set of special electrodes were developed for best performance (see Figure 2.)



**Figure 2.** The electrode setup for penile treatment of Peyronie's disease

## Protocol of treatments

The proposed and tested protocol of treatment was made 30 min two times a week, overall treatment number was 30 treatment/case in 3 cycle (10 sessions in each). One of the actual treatment setup is shown in Figure 3.



**Figure 3.** The fit of the electrode on the penis during the treatment

The treatments were used only as monotherapy, studying first the effect on the new method alone. All the Patients were advanced stages, and their symptoms were measured in standard methods.

The practical parameters to observe the expected changes were:

- Size plaque
- Curvature of the penis
- Pain reduction at erection
- Erection function

## Results

30 Patients were studied: one of them was withdrawn, 5 patients have not completed the whole course of treatments, at present we have the final data of 22 Patients. The age distribution was shifted to elderly categories (between 65 and 70 years ). The plaque size decreased, after the treatments, about 50%, the Figure 4. Shows the plaque size before and after Androthermia. We evaluated the extendt of the plaques with ultrasound scans before and after the treatments.

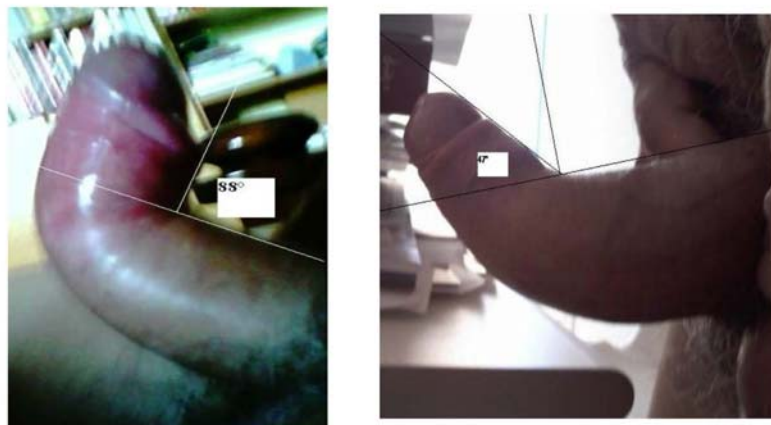
### PLAQUE SIZE

Dataset	1	2
Number in sample	22	22
Average	12,2818	6,2136
Standard Dev.	7,2447	4,3274
<b>t</b>	<b>3,3728</b>	
<b>gradi di libertà</b>	<b>42</b>	
<b>P ( level of significance )</b>	<b>0,0016</b>	

The difference between the observed means is significant for  $p < 0,01$

**Figure 4.** The plaque size reduction after Androthermia

Only 15 Patients had curvature of the penis during erection, Figure 5 shows the average of curvature of the penis before and after Androtherm treatment. We estimated the curvature degree of the penis, during erection, before and after treatments, with a goniometer ( Figure 5 shows our method of measurement in a Patient with a curvature very noticeable ).



**Figure 5.** Patient with an extreme curvature of the penis, before and after treatment

#### CURVATURE OF THE PENIS

Dataset	1	2
Number in sample	15	15
Average	35,8000	23,6667
Standard Dev	16,3016	10,1236
<b>t</b>	<b>2,4489</b>	
<b>gradi di libertà</b>	<b>28</b>	
<b>P ( level of significance )</b>	<b>0,0209</b>	

**The difference between the observed means is significant for  $p < 0,05$**

**Figure 6.** Results on curvature

10 Patienti reported the coexistence of an erectile dysfunction which was evaluated by the administration of questionnaires IIIEf 5, 15, before and after the treatments. Figure 6 shows the improvement of sexual performances obtained after treatments with Androthermia.

# ERECTIL DISFUNCTION

Dataset	1	2
Number in sample	10	10
Average	46,1000	57,5000
Standard Dev	13,5438	9,5248
<b>t</b>	<b>2,1772</b>	
<b>gradi di libertà</b>	<b>18</b>	
<b>P ( level of significance )</b>	<b>0,0430</b>	

**The difference between the observed means is significant for  $p < 0,05$**

**Figure 7.** Improvement of the average IIEF

All Patients who presented with pain during erection, reported the complete disappearance of symptoms.

## Conclusions

Based on the results obtained we can say that the ANDROTHERMIA can be considered a very promising new therapy for the treatment of Peyronie's disease. The study is still in progress and the results of new cases in treatment confirm the validity of the method. The data until now obtained, could pave the way for new therapeutic approaches for others diseases of the penis.

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