DATA: Hormone Therapy with Pellet Implants

Hormone replacement therapy by pellet implantation has been used with great success in the United States, Europe and Australia since 1938 and found to be superior to other methods of hormone delivery (Greenblatt 49, Mishnell 41, Cantrill 84, Stanczyk 88). It is **not** experimental. Pellets deliver **consistent**, physiologic levels of hormones and avoid the fluctuations of hormone levels seen with other methods of delivery (Greenblatt 49, Thom 81, Cantrill 84 Stanczyk 88).

Hormones delivered by the subcutaneous implants bypass the liver, do not affect clotting factors and do not increase the risk of thrombosis (Notelovitz 87, Seed 00). Bioidentical testosterone delivered subcutaneously by pellet implant is cardiac protective, unlike oral, synthetic testosterone (Sands 97, Worboys 00).

Testosterone delivered by pellet implantation, does not adversely affect blood pressure, lipid levels, glucose or liver functions (Burger 84, Farish 84, Fletcher 86, Barlow 86, Notelovitz 84, Stanczyk 88, Davis 95, 00, Handelsman 96, Sands 97, Seed 00, Cravioto 01). In addition, testosterone is a vasodilator (Perusquía 10).

Pellets are **superior** to oral and topical hormone therapy with respect to relief of menopausal symptoms (Staland 78, Cardoza 84). Testosterone implants have consistently been shown to improve insomnia, sex drive, libido, hot flashes, palpitations, headaches, irritability, depression, aches, pains, and vaginal dryness (Glaser 11, Staland 78, Thom 81, Brincat 84, Davis 95, 00, Cravioto 01).

Hormone replacement therapy with estradiol and testosterone implants is **superior** to oral and topical (both the patch and gel) hormone replacement therapy for **bone density** (Savvas 88, 92, Davis 95, Anderson 97). The **consistent, adequate** levels of testosterone delivered by pellet implant are important in maintaining bone mineral density (Aminoroaya 05) while also being available as a substrate for the production of estradiol (Simpson 02, 03). The pellets not only prevent bone loss, they actually **increase** bone density (Savvas 88, Studd 90, Garnett 91, Savvas 92, Naessen 93, Holland 94, Studd 94, Davis 95, Anderson 97, Seed 00, Panay 00).

Testosterone implants in women have been shown to improve lethargy, depression, loss of libido, and hot flashes without attenuating the beneficial affects of estradiol on cardiac and lipid profiles (Farish 84, Fletcher 86, Sands 97, Seed 00). Testosterone, delivered by pellet implant does not affect the menstrual cycle (Dewis 86) and has been used to treat endometriosis and uterine fibroids (Greenblatt 49). Testosterone pellet implants have also been used to successfully treat severe pre-menstrual syndrome unresponsive to other forms of therapy, without adverse effects (Dewis 84).

Testosterone, delivered by subcutaneous pellet implant has been shown to improve hot flashes, heart discomfort, sleep problems, depressive mood, irritability, anxiety, physical fatigue, memory loss, migraine headaches, sexual problems, bladder problems (incontinence), vaginal dryness, joint and muscular discomfort in both pre-menopausal and post-menopausal patients without adverse drug events (Glaser 11).

Pellets do not have the same risk of breast cancer as the synthetic progestins or synthetic Methy-testosterone. In fact, studies show a **reduction** in the incidence of breast cancer with the implantation of **testosterone** pellets (Dimitrakakis 04, Tutera 09).

Even after over 20 years of therapy with hormone implants, the risk of breast cancer is not increased (Gambrel 06). In breast cancer survivors, hormone replacement therapy with pellet implantation does **not** increase the risk of cancer recurrence or death (Natrajan 02) as does estrogen in combination with the synthetic progestins (Habits Trial 04). Hormone replacement therapy with testosterone pellet implantation has an extremely low incidence of side effects (Glaser 11) and high compliance rate (Gambrell 06).

Testosterone replacement therapy in men with subcutaneous implants (pellets) has been show to be effective, convenient and safe (Handelsman 90, 92, 97, Kelleher 01, 04, Conway 88, Jockenhoval 96, Zacharin 03, Schubert 03, Dunning 04).

The testosterone implant is licensed in England for women. The 75 mg testosterone implant is FDA approved in the US (July 13,1972, male patients). Other doses need to be compounded by trained pharmacists.

> The *75 mg pellet* is a sterile product is cylindrically shaped and weighs approximately 77mg (75mg testosterone). The inactive ingredients include 0.2mg stearic acid USP and 2mg polyvinylpyrroidone USP.

The routine doses of testosterone delivered by pellet implantation in recent studies are between 800 and 1200 mg in men. The pharmacokinetics and pharmacodynamics are well established showing that these doses deliver reproducible physiologic levels of testosterone for 4-6 months. The studies show that pellets have a zero order release rate. Although individuals vary, the 75 mg testosterone pellet has a consistent release rate approximately 0.5 mg of testosterone per day for a total of approximately 6 mg per day for 12 pellets. A 6-9 mg daily production of testosterone is a 'physiologic' level produced by the testicles.

Testosterone implants have a near linear release rate. Peak serum testosterone levels with the implants are usually seen at month one. Therapeutic testosterone levels at month one, are expected at the upper limits of normal for healthy young males (800-1100 ng/dL). By month 4 to 5 testosterone levels drop to below 500-600 ng/dL at which time symptoms return and the pellets are reinserted. Each individual has their own reproducible levels where symptoms return.

Testosterone implants have been used in women. Doses used in studies are as low as 50 mg and up to 225 mg. In the United States, common doses are100 to 225 mg. There are minimal side effects at these doses (an increase in facial hair and mild acne), which may be reduced by lowering the dose, if the patient chooses. If measured, serum treatment levels are elevated above non-treatment levels at month one (Burger 84, Dewis 84, Gambrel 06, Thom 81, Glaser 09). Urine and saliva levels remain normal. There are no signs of androgen excess at these treatment levels. Symptoms return when testosterone levels reach the upper end of endogenous ranges (Burger 84). End organ response to testosterone remains optimal (i.e., relief of depression, increase in bone density, relief from insomnia, relief from aches and pains, lessened anxiety, improved memory and concentration, increased energy, etc.). Testosterone implants last between 2.5 and 5 months in female patients. Individual treatment doses and treatment ranges are established and are reproducible. Long-term studies with up to **30 years** follow up, confirm the safety of testosterone therapy and absence of adverse drug events with the pellet implant (Gambrel 06, Traish10).

In a paper published in the journal 'Menopause' in 2004, '*Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy'* women were referred for testosterone supplementation for the following indications:

- Complaints of emotional lability
- Fatigue and loss of stamina
- Impaired concentration and memory
- Breast tenderness
- Loss of libido

- Sleep disturbance
- Muscle weakness

Patients received testosterone implant containing 50-150 mg of testosterone every 5 months in addition to conventional estrogen or estrogen/progestin therapy. The testosterone dose was titrated to alleviate symptoms (listed above), **improve bone mineral density** and minimize adverse affects (slight increase in facial hair and acne).

The addition of testosterone, delivered by pellet implant, was shown to reduce the incidence of breast cancer in women treated with conventional hormone therapy. In women, not on synthetic progestin therapy (which is known to increase the incidence of breast cancer RR 1.69-2.00), the incidence of breast cancer was lower than 'no hormone therapy'.

Testosterone therapy alone, delivered by pellet implant is effective for the relief of both physical and psychological symptoms in **pre-menopausal and post-menopausal** patients. Symptoms of testosterone deficiency/hormone imbalance are often seen prior to menopause. Many women begin to experience symptoms by age 35-40, when testosterone production has declined by half (Zumoff 95).

Testosterone alone has previously been reported to be more effective than estrogen/testosterone or estrogen therapy for relief of somatic and psychological symptoms (Sherwin 85). Uninterrupted sufficiency of circulating testosterone supports the production of estradiol by aromatase in estrogen dependent tissues (brain, bone, muscle, skin, cardiac, vascular tissue, fat and breast tissue) and affords protection against estrogen deficiency. Also, low circulating levels of estrogen have no bearing on estrogen produced locally. This may explain why **continuous delivery** of testosterone by pellet implant is so effective in post-menopausal patients.

Subcutaneous testosterone therapy is **safe** and extremely **effective** in pre and post-menopausal patients as well as men.

For additional information on the benefits of testosterone, please refer to:

Glaser R, York AE, Dimitrakakis C. Beneficial effects of testosterone therapy in women measured by the validated Menopause Rating Scale (MRS). *Maturitas*. 20011;68:355-361.

Abstract

Objectives

This study was designed to measure the beneficial effects of continuous testosterone therapy, delivered by subcutaneous implant, in the relief of somatic, psychological and urogenital symptoms in both pre- and post-menopausal patients, utilizing the validated Health Related Quality of Life (HRQOL), Menopause Rating Scale (MRS).

Study design

300 pre- and post-menopausal women with symptoms of relative androgen deficiency, were asked to self-administer the 11-item MRS, at baseline and 3 months after their first insertion of the subcutaneous testosterone implant. Baseline hormone measurements, menopausal status and BMI, were assessed to determine correlation with symptoms and clinical outcome.

Main outcome measurements

Changes related to therapy were determined. Total MRS scores as well as psychological, somatic and urogenital subscale scores were compared prior to therapy and following testosterone implant therapy.

Results

Pre-menopausal and post-menopausal females reported similar hormone deficiency symptoms. Both groups demonstrated similar improvement in total score, as well as psychological, somatic and urogenital subscale scores with testosterone therapy. Better effect was noted in women with more severe complaints. Higher doses of testosterone correlated with greater improvement in symptoms.

Conclusion

Continuous testosterone alone, delivered by subcutaneous implant, was effective for the relief of hormone deficiency symptoms in both pre- and post-menopausal patients. The validated, HRQOL questionnaire, Menopause Rating Scale (MRS), proved a valuable tool in the measurement of the beneficial effects of testosterone therapy in both cohorts.