Sub-Cutaneous Hormone Pellet Therapy - The Comprehensive Treatment to Optimize and Balance Hormones Using the BioTE® Method

Gary S. Donovitz, MD, FACOG

The BioTE® method of hormone replacement is a time tested method of hormone optimization that was created from the hundreds of studies performed on hundreds of thousands of patients worldwide to successfully optimize the hormone levels of women as they meander through the "seasons" of peri menopause and menopause and men as the traverse the "season" of andropause.

After monitoring outcomes for tens of thousands of men and women who have benefitted from this therapy, we have found results have been better than expected with more than 96% of patients satisfied and with side effects much less than that quoted in literature.

Hormone replacement therapy (HRT) is used to treat menopausal symptoms in women and andropause symptoms in males. Most women who take HRT for menopausal reasons are given an estrogen/progesterone/testosterone combination, except those who have had a hysterectomy, as they may not need progesterone. HRT has shown to reduce fatigue, improve sleep, improve libido in women and sexual performance in men, decrease muscle loss and reduce body fat (Staland 78, Thom 81, Brincat 84, and Davis 95). It also has been shown to reduce irritability, anxiety and depression. The symptoms of osteoarthritis and rheumatoid arthritis are significantly reduced. Long term, men and women will have reduced incidence of Alzheimer's disease, heart disease, and osteoporosis (Studd 90, Sands 97, Worboys 00). There are multiple studies showing the long term reduction in breast cancer in women using pellet therapy

(Notelovitz 04, Glaser 2013) 02) rather than the increase in the incidence of breast cancer that has been associated with oral, synthetic methyl-testosterone (Tamimi 06). Even after over 20 years of therapy with hormone implants, the risk of breast cancer is not increased (Gambrell 06).

Hormone replacement therapy by pellet implantation has been used with great success in the United States, Europe and Australia since 1938, and has been found to be superior to other methods of hormone delivery (Greenblatt49, Mishnell 41, 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 like pills, creams, gels and synthetic injections (Greenblatt 49, Thom 81, Stanczyk 88). Pellets are superior to oral and topical hormone therapy with respect to relief of menopausal symptoms (Staland 78, Cardoza 84).

Hormones delivered by the subcutaneous implants bypass the liver, do not affect clotting factors and do not increase the risk of thrombosis (Notelovitz 87).

Testosterone and estradiol delivered by pellet implantation, does not adversely affect blood pressure, glucose or liver functions (Burger 84, Barlow 86, Notelovitz 84, Stanczyk 88, Davis 95, Sands 97, Seed 00, Cravioto 01). In fact, testosterone and estradiol improved lipid profiles by reducing cholesterol, reducing triglycerides, and increasing HDL cholesterol (Davis 05). This has positive benefits on the cardiovascular system.

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 pellets not only prevent bone loss but also actually increase bone density (Savvas 88, Studd 90, Garnett 91, Savvas 92, Naessen 93, Holland 94, Studd 94, Davis 95, and Anderson 97).

Testosterone replacement therapy in men with subcutaneous implants (pellets) has been shown to be extremely effective, convenient and safe (Handelsman 90, 92, 97, Kelleher 01, 04, Conway 88,Jockenhoval 96, Zacharin 03, Schubert 03, Dunning 04). The continuation rate continues to be 93% or above. This is excellent for long term compliance and exceeds the continuation seen with all other treatments for andropause.

The routine doses of testosterone delivered by pellet implantation in recent studies are between 1000 and 2400 mg in men. The pharmacokinetics and pharmacodynamics are well established showing that these doses deliver reproducible physiologic levels of testosterone for 4-6 months. A 6-9 mg daily production of testosterone is a 'physiologic' level produced by the testicle. 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 (900-1100 ng/dL). These levels are necessary to protect the brain from Alzheimer's disease, diabetes, heart disease, prostate cancer, osteoporosis and all-cause mortality (Zitzman M. J Clin Endocrinology 2006). 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 in 5 continents for decades. Doses used in studies are as low as 50 mg and up to 225 mg Glaser and Dimitrakakis Maturitas: 2004). Normal testosterone levels are not established in females (Fertility and Sterility 2002). Symptoms return when testosterone levels reach the upper end of endogenous ranges (Burger 85). 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.) when testosterone levels at 4-6 weeks after pellet insertion are 150-250 ng/dL. Steady state is subsequently achieved at approximately half of these levels equaling 80-120 ng/dL, which is in the physiologic to slightly supra-physiologic range. It is of primary importance to titrate the dose to achieve symptom relief and minimize side effects, not to achieve some phantom blood level. As women age, testosterone

receptors become less responsive and more often than not, higher levels of testosterone are required to achieve the clinical outcome desired of symptom relief and long-term protection to the brain, breast, heart and bones. Some women require upwards of 300 ng/dl to achieve these results. Side effects from testosterone therapy in women are more of a nuisance and are reversible; there are no known long-term adverse effects in women, even at supra-physiologic levels.

Patient compliance becomes a non-issue using the pellet modality.

The method of sub-cutaneous hormone replacement therapy has been consistent throughout the literature. What was needed was a refinement of the pellets themselves. BioTE® Medical has established the "gold standard" in pellet preparation. We standardized the process and then used independent labs to assure proper density, purity, potency, sterility, dissolution rate, solubility and temperature tolerance; all of which significantly affect how well a patient responds to the therapy. This extensive safeguard allows us to supply pellets with only 3% tolerance for potency (i.e. our pellets when prescribed will nearly match that requested). This is in contrast to prescribed pills and creams which may have 10-30% tolerance. We use no fillers in our compounded pellets and as such purity testing is superior. No pellets are dispensed until sterility is certified and assured.

The literature is substantial supporting sub-cutaneous hormone pellet therapy as the superior method of hormone replacement in men and women. By using the BioTE® dosing site (which is based on 30 years of clinical experience), by using the highest quality pellets made in the United States, and by continuing to educate, supervise and monitor all BioTE® practitioners, we at BioTE® have made pellet therapy the superior method now scalable to practitioners and patients across the country. This has established the new standard of care for HRT.

BioTE® has created innovative and industry leading protocols and processes in properly balancing hormones using not only Estradiol, Testosterone, and Progesterone, but also natural support supplements like Vitamins A, D, &K, Iodine and DIM. The BioTE® Method also aggressively treats thyroid conditions, as those contribute greatly to overall hormone balance and the well-being of the patient. All serum levels are tracked pre and post insertion as well as annually.

BioTE® tracks and monitors nearly 100,000 procedures performed annually by our network of Certified Practitioners throughout the United States and Puerto Rico. Any and all complications that may arise are also tracked and include conditions such as breast cancer, stroke, heart attacks, DVTs, endometrial cancer and prostate cancer.

Finally, BioTE® recognizes there are many medical practitioners that are "experimenting with pellet therapy," and they have had varied (sometimes even disastrous) results. After all, the only thing between medicine and poison is the dose (Aspirin can be bad if taken improperly). However, BioTE® provides all of our practitioners extensive clinical and didactic training, as well as 24/7 dosing support thus ensuring the highest safety and efficacy and results for our patients.

For more info on BioTE® Medical please contact info@biotemedical.com or visit www.biotemedical.com

Articles on Pellet Hormone Delivery System

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2. Use in America since 1949
    i. Greenblatt: AJOG. 1949
3. All estrogen and estrogen/synthetic progestin Increase risk of Breast Cancer
    a. Million Women Study
        i. Lancet.2003
4. Estrogen and Testosterone does not increase risk of Breast Cancer
    a. Nurses' Health Study
        i. Colditz:NEJM.1995
5. Non Oral (Pellets) testosterone prevents stimulation of breast tissue and lowers risk of Breast Cancer
    i. Colditz: Archives of Int Med.1996
6. Osteoporosis: Pellets increase bone density by 8.3 % per year vs. oral estrogen 1-2%increase per year
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7. Improved Lipid Parameters: Decreased Cholesterol, Decrease TG, Increased HDL
    i. Susan Davis: Menopause Vol 7
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    i. Smith: Br. Med Journal. 1993
9. Cardiovascular Benefits: Decrease death Rate by increasing testosterone
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    i. Stancyk: AJOG.Vol 159
12. Hormones Ease Pain of Osteoarthritis
    i. Arthritis and Rheumatism. 2010
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    i. Cravioto: Menopause.2001

Breast Cancer and the Hormone Recepter Model - A White Paper Monograph

Gary S. Donovitz, MD and Mandy Cotten, DNP

Introduction

In the United States, 240,000 women will develop breast cancer annually and 40,000 will succumb to the disease. Additionally, there are an estimated 63,960 cases of in-situ disease in the United States in 2018 (Seigel et al., 2018, National Cancer Institute, 2018).

We know that one of the greatest fears for women as their endogenous hormone production wanes and they explore the thought of requiring hormone replacement therapy is breast cancer (Walsh-Childers, Edwards & Grobmyer, 2011). Inadequate knowledge surrounding the effects of circulating hormone levels on breast cancer is fairly consistent throughout the medical community. At BioTE®, as we have surpassed 1 million pellet insertions, using both testosterone and/or estradiol hormones, the incidence of breast cancer in both pre-and post-menopausal women among our more than 3,500 providers remains remarkably low. Our experience invites one to ask the obvious question, can hormone optimization using subcutaneous hormone pellets reduce the incidence of breast cancer? If so, what is the likely mechanism for this? And finally, can testosterone pellet therapy be used safely and therapeutically in breast cancer survivors? In order to adequately be able to answer these questions, providers must understand several factors: screening, classification of breast cancer, and genetic markers that increase risk.

Screening

Before we answer these questions, we need to review the screening recommendations and breast cancer classification. The United States Preventative Services Task Force reported in 2016 that they no longer recommend clinical breast exams., Likewise, the American Cancer Society in 2015 no longer recommends clinical breast exams. Mammogram recommendations vary from ACOG, USPTFS, and the American Cancer Society. In general, providers should be recommending mammograms starting by the age of 50 and continuing annually or biennially until the age of 75 if the patient is of average risk (National Cancer Institute, 2018, ACOG, 2017).

Breast Cancer Classification

The classification of invasive breast cancer is important to understand before we overlay the hormone receptor theory and then apply the mechanism by which testosterone protects the breast tissue from cancer.

Breast cancer is classified based on breast cancer type, grade, molecular subtypes, and stage (Onitilo et al., 2009). The type of breast cancer is based upon location and aggressiveness of the disease. Invasive breast cancer is a heterogeneous disease presenting most often as invasive ductal carcinoma in 75% of cases. Lobular carcinoma, inflammatory carcinoma, and Paget's disease of the nipple occur less frequently (Onilio et al., 2009; Breastcancer.org, 2018).

The grade of the cancer is based upon how the tissue appears on biopsy and how fast the cells grow. Invasive ductal carcinoma has five molecular subtypes, and in general tends to be low grade, and less aggressive. Molecular subtypes are very important in determining the treatment plan and risk profile for the patient. The subtypes include luminal A, luminal B, triple negative/ basal like, HER2 (Human Epidermal Growth Factor Receptor 2) enriched, and normal like (Longo, Fauci, Kasper, Hauser, & Jameson, 2011, Breastcancer.org, 2018).

Luminal A has the highest level of estrogen receptor expression and are most likely to respond to endocrine therapy such as tamoxifen and aromatase inhibitors. In addition, this type of tumor is typically HER2 negative. The intracellular protein Ki-67, a protein identified with ongoing proliferation is low, and overall they have an favorable prognosis despite being less responsive to chemotherapy (Longo et al., 2011, Breastcancer.org, 2018).

In luminal B tumors, prognosis is worse than with Luminal A. Ki-67 protein is higher, consistent with increased proliferation. Hormone receptors are often positive and can also be HER2 receptor protein positive. Twenty percent of breast cancers have the gene mutation that makes excessive HER2 protein. Luminal B tumors subsequently grow faster than luminal A tumors. They often fail existing treatments and have lower 5- and 10-year survival (Longo et al., 2011, Breastcancer.org, 2018, Cheang et al., 2009).

The triple negative basal-like tumors account for 15-20% of all breast cancers and are devoid of estrogen, progesterone, and HER-2 receptors. They are more common in BRAC 1 gene mutated patients. These aggressive tumors respond better to chemotherapy and can have a binary response to androgens, which will be discussed further (Longo et al., 2011, Breastcancer.org, 2018).

HER2 enriched tumors account for 15 percent of breast cancers. They are estrogen and progesterone receptor negative, but HER2 positive. They are faster growing and more aggressive than their luminal tumor counterparts. These tumors frequently metastasize to the brain and unfortunately the anti-HER2 antibodies do not cross the blood brain barrier (Leylan-Jones et al., 2009). Treatment usually includes trastuzamab (Herceptin), which

targets the HER2 protein (Perou et al., 2000).

Normal-like tumors are similar to luminal A disease: hormone-receptor, HER2 negative, and low levels of the protein Ki-67. These tumors have a good prognosis, but slightly worse than luminal A (Longo et al., 2011, Breastcancer.org, 2018).

BRCA1 and BRCA2 Mutations

There are several genetic mutations that increase the risk of developing breast cancer. Probably the most well known and reported on are the mutations of the proteins BRCA1 and BRCA2. These proteins, like the metabolite 2-OH estrone, are involved in DNA repair. When either of these genes is mutated, or altered,

such that its protein product is not made or does not function correctly, DNA damage may not be repaired properly. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer.

Women without the BRCA mutation have a 12% lifetime risk of developing breast cancer, and the average age for developing breast cancer in the BRAC (-) women is 61 years old (Howlader et al., 2018). With a mutation in the BRCA gene, the incidence of breast cancer increases to 60-80% and the average age of development decreases to 42 years old (Nathanson et al., 2001). Patients with BRCA 1 and BRCA 2 mutations also have a 20-40% chance of developing cancer in the same or contralateral breast in the years following diagnosis (Kuchenbaecker, Hopper, Barnes, et al., 2017 & Metcalfe et al., 2014).

The USPSTF recommends genetic screening for patients who have a significant family history such as: breast cancer diagnosis prior to age 50, cancer in bilateral breasts, family history of both breast and ovarian cancer, multiple family breast cancers, two or more primary BRCA1 or BRCA2 related cancers in same family member, male breast cancer, and Ashkenazi Jewish ethnicity (USPSTF, 2013). Breast cancers in patients with BRCA1 mutation tend to be triple negative.

A class of drugs called PARP (poly ADP ribose polymerase) inhibitors, which block the repair of DNA damage, have been found to help prevent the proliferation of cancer cells that have BRCA1 or BRCA2 mutations. Also, research has shown that prophylactic mastectomy and oophorectomy in these patients can increase their lifespan by up to six years (Grann et al., 1998).

Clinical Evidence, Breast Cancer, & the BioTE® Method

Evidence supports the use of the BioTE® method of hormone optimization to reduce breast cancer. The risk of developing breast cancer has been shown to be increased by elevated endogenous estrogen levels (Henderson, 2000). In addition, androgens have been shown to counteract the proliferative effects of estrogen and progestogen in mammary tissue (Ando, 2002). Breast tissue extirpated from pre-and post-menopausal women also demonstrated the inhibitory effects of testosterone on breast cell proliferation (Hofling et al., 2007 & Dimitrikakis et al., 2003).

The corollary has also been reported that bio-available testosterone is significantly lower in women with breast cancer, which supports the protective role that hormone optimization with testosterone affords to patients (Dimitrakakis et al., 2010). Adherence to testosterone hormone pellet therapy has furthermore shown to reduce the incidence of breast cancer from 243 per 100,000 women years (placebo arm of the Women's Health Initiative) to 73 per 100,000 women years in the Dayton study in the subset of patients receiving testosterone or testosterone with anastrozole subcutaneous hormone pellet therapy (Glazer, 2013). At BioTE® using testosterone and/or testosterone and estradiol pellets in our observational prospective self- reporting study, the incidence of breast cancer was 56 per 100,000 women years after nine years of follow-up. (In Press).

Clinical Evidence & The Hormone Receptor Model

Now we will discuss the clinical evidence supporting the hormone receptor model specifically targeting the androgen receptor. The benefits of the afroementioned testosterone optimization are both exciting and life-changing to women's healthcare. Even more exciting is the genesis of why this therapy reduces the incidence of breast cancer and why it has therapeutic implications for patients who are afflicted with the disease. A review of the history of androgen therapy reveals that testosterone and dihydrotestosterone were used successfully to treat breast cancer in the 1940s and 1950s (Hermann et al., 1946; Adair et al., 1946). Unfortunately, inaccurate dosing not individualized to the patient leads to masculinizing side effects. Now, decades later, the discovery of tamoxifen and aromatase inhibitors were thought to be better alternatives for the commercialization of breast cancer therapy with little thought being given to breast cancer prevention.

Over the past decade and a half, Dr. Ed Friedman has performed extensive research on the hormone receptor model published in 2013 (Friedman, 2013). The hormone receptor model is centered around the fact that endogenous serum estradiol levels are not the initiators of breast cancer but rather increased aromatase activity leading to high local levels of estradiol in epithelial cells and surrounding fat cells influence disease development. High levels of estradiol in the cells activate the ER alpha receptor, increasing proliferation, lengthening chromosomal telomeres, and increasing BCL-2 protein leading to further accelerated proliferation of the cancer cells. In addition, the high levels of local estradiol increase 4-0H estrone, which is known to be mutagenic and causes DNA damage. Once the right mutation occurs, the mutagenesis and proliferation cause excessive cell growth overtaking compensatory cell death. In other words, apoptosis is significantly reduced. In the past, HRT containing synthetic progestins accelerated this process by reducing the doubling time of tumors by 25% (Santen et al., 2012).

The hormone receptor model also helps to explain why progesterone may be harmful rather than protective in breast tumors occurring in patients with the BRCA mutated gene. Considering there are two progesterone receptors in breast tissue progesterone alpha and progesterone beta and their effect on proliferation is quite different. The normal breast cell has a predominance of progesterone beta receptors allowing for endogenous and exogenous progesterone to inhibit proliferation and reduce BCL2 protein, and thereby confer protection to the breast. In patients with the mutated BRCA gene there are almost no progesterone beta receptors. This occurrence allows for expression of progesterone alpha receptor which increases proliferation, telomere length, and BCL2 protein. BCL2 protein allows cancer cells to live

longer and avoid apoptosis. Testosterone works by binding to the androgen receptor and downregulating the estrogen alpha receptor (Collins et al., 2011; Peters et al., 2009).

Surprisingly, the androgen receptor is the most widely expressed nuclear hormone receptor in the breast (Agrawal 2008). The intracellular androgen receptor is present in 77% of breast cancer tumors. In luminal A tumors, 91% have the androgen receptor, while it appears in 68% of luminal B tumors, and 59% expression in HER2 subtype tumors (Narayanan & Dalton, 2016, Dimitrakakis et al., 2004). Studies show an inverse relationship between tumors that possessed the androgen receptor and the size, grade, and lymph node status. On the contrary, tumors lacking an intracellular androgen receptor were mostly found to be grade 3 (fast growing, poorly differentiated cells).

The BioTE® Method of hormone optimization capitalizes on the tumoricidal effects of the activated androgen receptor. Most post-menopausal breast cancers are estrogen receptor positive and 75% of these tumors are androgen receptor positive, allowing for us to increase apoptosis and decrease cellular proliferation. In addition, cancers with the androgen receptor expression have improved overall survival and disease-free survival (Vera-Badillo et al., 2014). Not only is the androgen receptor associated with smaller tumors, that are less aggressive, and lower grade, but also has been shown to be associated with lower risk of recurrence (Qu et al., 2013). The androgen receptor is also an excellent predictor of therapeutic response to tamoxifen. In patients who are androgen receptor negative, the response to tamoxifen is worse (Hilborn et al., 2016).

Now, we must discuss triple negative breast cancer. A study specifically looking at triple negative breast cancer and the androgen receptor showed that the androgen receptor expression when present reduced recurrence and reduced the incidence of death (Agoff et al., 2003). In estrogen receptor negative (Er-), HER2 positive breast cancers, markers of proliferation like Ki-67 and carbonic anhydrate were lower if there were androgen receptors expressed, which was also associated with longer Disease-Free Survival (DFS) and Overall Survival (OS). Impressively, 59% of triple negative breast cancers are androgen receptor positive and therefore a target rich environment for testosterone optimization (Noh et al., 2014). Taking testosterone optimization and breast cancer therapy one step further, if the tumor cells have androgen synthesizing enzymes (i.e. capable of making testosterone and DHT intracellularly) and have androgen receptor expression, then proliferation markers as described above are negatively correlated and survival is shown to be better (McNamara et al., 2013).

One should also consider the intracrine androgen synthesis which occurs in breast cancer cells. Higher intracellular androgen concentrations in estrogen receptor positive tumors are strongly associated with better prognosis and a more favorable OS and DFS (Choi, 2015). What is not discussed in this article but is thought- provoking is the membrane androgen receptor, which is completely different from the intracellular androgen receptor. The membrane androgen receptor increases pro-apoptotic proteins and decreases BCL2 protein accelerating cell death in breast cancer cells. This is the essence of the hormone receptor model postulated by Ed Friedman, PhD (2013).

Although, the majority of studies portend the benefits of the androgen receptor in the prognosis of breast cancer, there have been a few studies whereby there was a decrease in disease free survival (DFS). This most notably occurs in triple negative breast cancers and may be the result of a mutated gene leading to a mutated androgen receptor (Lehmann, 2014). In these somewhat more limited cases, an androgen antagonist is a better choice for therapeutic intervention.

Conclusion

In conclusion, it appears that the fears of developing breast cancer with usage of hormone replacement therapy are unwarranted, as the cancer could potentially be prevented by proper hormone optimization especially with the inclusion of testosterone. For those women whose lives have been compromised by breast cancer, hormone optimization with testosterone may not only improve their quality of life but also may be the therapeutic answer to improving their overall survival and defeating the cancer.

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