State-of-the-Art Subcutaneous Bioidentical Hormone Pellet Therapy

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ABSTRACT

The aim of this paper is to offer the reader an introduction to the many benefits of bioidentical hormone pellet therapy.

INTRODUCTION

In recent years, hormone therapy has been erroneously portrayed as being a somewhat risky treatment, and has been linked to all sorts of problems. However, the latest research into bioidentical hormone pellet therapy has sent those rumors back to where they belonged. Indeed, the intention of this paper is to demonstrate that hormone therapy is actually incredibly helpful, very safe, minimally risky, and can dramatically change a person's life.

When discussing hormone therapy it is very important to distinguish between bioidentical hormones and conventional hormones. Estrone (E1), 17 beta-estradiol (E2), estriol (E3), progesterone, and testosterone are bioidentical hormones – meaning that the molecular shape of these hormones is identical to the hormone made by the body. For reasons unknown, conventional medicine decided to use non-bioidentical hormones for hormone replacement. Commonly used non-bioidentical hormones include:

- Conjugated equine (or horse) estrogens (CEE);
- Progestins – synthetic progesterones, which are known carcinogens;
- Methyltestosterone.

None of the above non-bioidentical hormones are native to the body. They are not the same hormones. In fact, they are not even hormones, they are drugs. Hormones are natural to your body, they are a natural treatment.

BIOIDENTICAL HORMONE PELLET THERAPY

A Brief History of Bioidentical Hormone Replacement Therapy

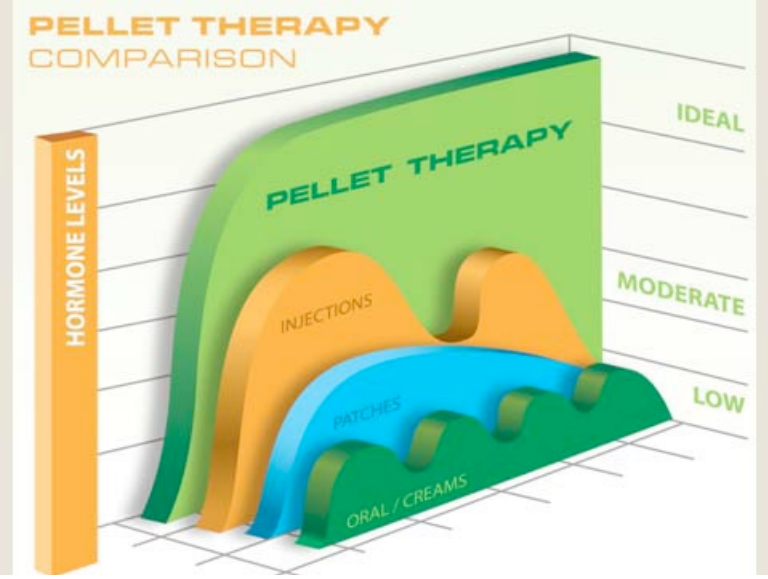
In 1917, a man named John Brinkley claimed that he was a physician (he was not). Using fake credentials, he persuaded local farmers in Kansas and Texas to breed goats. He would then bring male goats into his clinic pen and have his male patients (who came from all over the United States) to select the most rampant looking goat. Then, on the day of surgery, he would castrate the unfortunate goat and implant its testicles into the man. Remarkably, it did work for some of the men. Somehow, they survived the procedure, and they derived some benefits from the goat's hormones. However, a lot of men died and ever since hormone replacement therapy has often been associated with quackery and people tend to be suspicious of it.

So, we can see that the idea of hormone replacement is not a new one. In the early 20th century hormones were a focus of medical research. In 1929, using urine obtained from pregnant women, Adolf Butenandt and Edward Adelbert Doisy independently isolated and determined the structure of estrogen.[1] This discovery was closely followed by that of aldosterone in 1931, also by Butenandt, but this time he was partnered with Kurt Tscherning.[2] Butenandt is also credited with the discovery of the structure of testosterone in 1935. Following this discovery, the chemical synthesis of testosterone from cholesterol was achieved in August that year by Butenandt and Hanisch.[3] Just one week later, Leopold Ruzicka and A Wettstein, published their synthesis of testosterone.[4] These independent partial syntheses of

testosterone from cholesterol base earned Butenandt and Ruzicka the joint 1939 Nobel Prize in Chemistry. These discoveries led the pioneering gynecologist Robert Greenblatt to begin researching and implanting testosterone pellets in 1939. In 1949, he added a lit bit of estradiol to improve symptom control. In 1972, the US Food and Drug Administration (FDA) approved the use of 75 mg testosterone pellets (Testopel®) in men. Note: If you use a dose higher than 75 mg it will be off-label, and if you use testosterone to treat women it will also be off-label. However, because it is FDA-approved you can use it off-label without significant concern. In Europe and Australia, 100 and 200 mg pellets are available.

Pellets: An Introduction

Pellet therapy is the gold standard of bioidentical hormone therapy. Why? There are many reasons as to why pellet therapy is superior to other forms of hormone delivery; however the main reason is that pellets deliver a constant level of the required hormone. This is illustrated in Figure 1.



As can be seen, within a couple of weeks of being implanted, pellets deliver an almost constant supply of hormones, which is similar to testicular or ovarian output. There are no peaks and valleys in hormone levels, like those created with injections, oral delivery, or creams. Hormone patches give you a more steady supply, but achievable hormone levels are not as high and patches often irritate the skin.
Exactly what are pellets? Pellets are made up of hormones (i.e. testosterone, estradiol) that are pressed or fused into very small sterile solid cylinders. They also contain a small amount of stearic acid. Most pellets are larger than a grain of rice and smaller than a 'Tic Tac'. When placed under the skin they consistently release small physiologic doses of hormones.
The idea of using pellets to deliver hormones is far from new. In fact, the original research into pellets was conducted way back in 1949 by Greenblatt and Suran.[5] Greenblatt proved that "…implantation of hard compressed pellets of crystalline steroids resulted in a slow and more physiologic absorption of the hormone...".[5] The authors also noted that pellets appeared to deliver hormones in a way similar to endogenous hormone secretion:

"Since the amount of hormone released to the organism is continuous though minute in quantity, it is conceivable that by this method the endogenous mechanism of hormonal secretion is more nearly approached and the physiologic action of the hormone more closely imitated."[5]

What does a pellet look like? This is illustrated in Figure 2. We can see that pellets are significantly smaller than quarters. They vary in size depending upon the dose being delivered. Estradiol pellets are the smallest and contain anywhere from 6 mg to 25 mg. The small size of estradiol pellets, especially 6 mg pellets, can prove awkward as they are very easy to drop. As can be seen, testosterone (60 mg) and anastrozole (4 mg), pellets are quite small as well. Testosterone pellets contain doses between 25 mg and 200 mg. The testosterone pellet shown in Figure 2 is a 200 mg pellet and that is the largest pellet that is currently made. While pellet therapy is advancing all the time, the size of the pellet is not going to change much because the size is determined by the amount of hormone present.

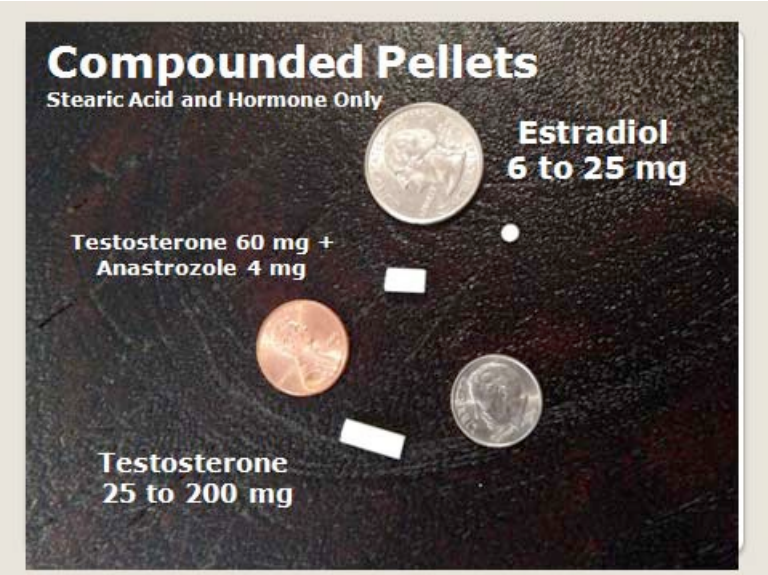


Figure 2. Pellet size varies and is determined by the amount of hormone present.

Factors to Consider

If you are considering using testosterone pellets it is important to be aware that testosterone can sometimes be converted by aromatase to estradiol (E2), which in turn converts to estrone (E1) – albeit reversibly, and estriol (E3). This is illustrated in Figure 3. However, for the purposes of pellet therapy, all you need to know is that testosterone is converted to estradiol (E2) by aromatase.

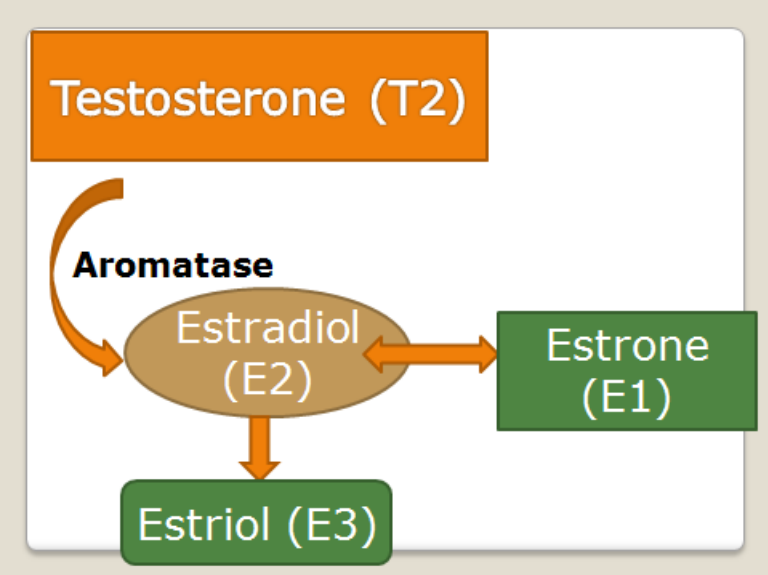


Figure 3. Testosterone can be converted to estradiol by the enzyme aromatase.

What is aromatase? Aromatase is an enzyme involved in the biosynthesis of estrogens. Aromatase can be helpful, but for the most part it causes problems. A multitude of factors can increase or decrease aromatase activity. Both genetics and aging are associated with increased aromatase activity; however there is nothing we can do about either of those things. However, a number of modifiable factors are known to increase aromatase activity, these include:

- Obesity (abdominal);
- Insulin resistance;
- Processed carbohydrates are among the worst refined foods in the genesis of insulin resistance. Eating a diet containing high levels of processed carbohydrates is also linked to elevated lipids (LDL cholesterol and triglycerides) and an increased risk of heart disease, diabetes, cancer, arthritis and pain, as well as depression and fatigue;
- Medications;
- Alcohol

The vast majority of patients you will see will be busily upregulating their aromatase activity through their lifestyle choices, their body composition, and their medications. So how can we decrease aromatase activity? Luckily, there are a number of things that can help to decrease aromatase activity, these include:

- Regular exercise;
- Eating a diet containing whole fresh foods with minimal toxic exposure, and which are preferably organic and/or free range;
- Aromatase inhibitors (anastrozole and letrozole) slow the activity of aromatase, and can be useful in patients who are taking medications, or who are overweight and/or have insulin resistance. They can also be of benefit to patients who are unwilling to reduce their intake of alcohol or carbohydrates;
- Indole-3-carbinol (I3C) a compound found in cruciferous vegetables, such as broccoli.

When treating women it is also very important to consider estrogen balance. Excess estrogen is associated with fluid retention, weight gain, abdominal fat, breast pain, anxiety, PMS, and uterine stimulation (bleeding, fibroids, endometriosis). Estrogen stimulates breast tissue and excess estrogen

may increase the risk of breast cancer long-term. Estrogen deficiency will cause menopause-like symptoms, for example hot flashes, insomnia, night sweats, vaginal dryness, and dry skin. Testosterone will often manage the symptoms of estrogen deficiency. If it doesn't, you will need to think about treating the patient with estrogen as well. It can be a delicate balance. One of the greatest problems we have in pellet therapy is estrogen stimulating a fibroid that has previously sat there quietly behaving itself. Giving such a patient too much estrogen will cause it to bleed, and leave you with another problem to deal with.

The Women's Health Initiative Study

Dr Greenblatt had been successfully treating women with bioidentical hormone pellet therapy since the 1930s, and this was doing wonders for the public perception of hormone replacement. Unfortunately, we then had the fallout from the Women's Health Initiative (WHI) study. The Premarin (conjugated equine estrogens) itself was not the problem. It was the progestin (synthetic progesterone) that was responsible for the really bad outcomes of this study. It is thought that the panic response to progestins and Premarin resulted in 40,000 preventable cardiovascular deaths. Had the data gathered from the WHI study been properly looked at in 2002 women would have been maintained on their hormone replacement therapy, some minus the progestin, and they would have been fine. Instead, we ended up with a panic situation that has left millions of women with intractable symptoms and unknown long-term osteoporosis issues.

The WHI study concluded that hormone replacement should only been given for 5-years at maximum. The authors also concluded that hormone replacement was associated with an increased risk of dementia and cardiovascular disease, and that bone is better left alone or treated with a bisphosphonate. Current data does not support any of these findings. In fact, current data has shown that bioidentical hormone replacement can be used lifelong, is safe and effective, and is associated with:

- Up to 7% increase in bone density per year;
- Improved anxiety and cognition;
- Decreased cardiovascular risk.

Benefits of Bioidentical Hormone Pellet Therapy

Bioidentical hormone pellet therapy is associated with numerous benefits, including:

- Increased libido and performance;
- Increased muscle – patients gain 4 lbs of lean muscle per year, on average;
- Decreased fat – patients lose 6 lbs of fat per year, on average;
- Increased bone density – as much as 7% per year;
- Heart protective – improves cardiac contractility;
- Coronary vasodilation – improves cardiac flow;
- Lowered breast cancer risk – by as much as 200-700%, meaning that the 24% lifelong risk of breast cancer for women is reduced to 4-5%;
- Relieved anxiety and depression;
- Relieves aches and pains;
- Lowers blood sugar;
- Neuroprotective;
- Restores memory;
- Improves the symptoms of neurodegenerative diseases, such as Parkinson's disease;
- Does not increase the risk of stroke – does not affect thrombotic activity because there is no first pass metabolism through the liver;

 Has no effect on the liver;

 Reverses incontinence – via plumping of the vaginal tissues (and anecdotally even relieves fecal incontinence in some people because of the muscle benefit);

 Restores sleep patterns;

 Thickens skin and reduces wrinkles.

Like with everything, there is the potential for some unwanted side effects. These include:

 Potential for allergic reaction;

 Potential for bleeding at incision site in patients taking blood thinning medications;

 Scarring – low risk, I have performed 8000+ implants but only needed to carry out 1 scar revision;

 Infection – may be an issue in 1 in every 150-200 procedures, easily treatable with antibacterial drugs;

 Acne – a common side effect in women with high-dose testosterone, reversible by lowering the dose of testosterone;

 Increased facial hair – another common side effect in women, reversible by lowering the dose of testosterone;

 Clitoral enlargement – reversible;

It is important to note that fetal masculinization in a pregnant woman is theoretical – there are no known cases of this.

Clinical Superiority of Pellet Therapy

Why is it better to use pellets instead of oral, injectable, or topical bioidentical hormones? Firstly, pellets are predictable – as mentioned previously, they deliver a constant physiologic dose of the required hormone(s). Secondly, there are no issues with compliance, once you have implanted the pellets you know the patient is 100% covered until their next visit. Thirdly, hormone secretion occurs on a demandresponse
basis. When metabolic rate increases (e.g. during exercise) and the demand for hormones rises, blood flow around the pellets increases and more hormone is absorbed. Conversely, when metabolic rate is slow (e.g. while sleeping) and less hormone is needed, blood flow around the pellet decreases and less hormone is absorbed. Fourthly, the problem of cross contamination is eliminated with pellets. With creams it is possible to give a loved one a dose of your hormones if you give them a hug. Finally, hormones released from pellets do not undergo first-pass metabolism.

Candidates for Bioidentical Hormone Pellet Therapy

Men and women of all ages can benefit from bioidentical hormone pellet therapy. You could treat an 81-year-old woman in order to reduce her risk of breast cancer and dementia, a 62-year-old woman to relieve the symptoms of menopause, and a 40-year-old woman in order to rid her of regular migraines. Men of all ages are candidates too. Children are obviously not candidates. Conditions which can be improved with bioidentical pellet hormone therapy include:

 Migraine;

 Fatigue;

 Hypoactive sexual desire/anorgasmia;

 Premenstrual syndrome (PMS);

 Incontinence (urinary);

 Osteopenia/sarcopenia;

 AIDS and immune imbalances;

 Depression/irritability and mood swings.

Evaluation for Bioidentical Hormone Pellet Therapy
Before starting treatment you need to carry out a thorough physical examination and take a detailed medical history. A comprehensive laboratory evaluation is also necessary. Laboratory evaluation for men should include:

 PSA (before rectal exam);

 Testosterone (total, free) – lower 1/3 of normal and symptomatic warrants treatment (variation throughout the day of 300 ng/dL);

 Sensitive estradiol – <5% of total E2;

 Complete blood count (CMC) with differential;

 Complete metabolic panel (CMP);

 Lipids (statins and other drugs);

 Ultrasensitive thyroid stimulating hormone (TSH), free T3 and free T4;

 Follicle stimulating hormone (FSH) and/or luteinizing hormone (LH);

 Sex hormone binding globulin (SHBG);

 Iron, ferritin.

Laboratory evaluation for women should include:

 Pap and mammogram;

 Testosterone (1-month peak) – a very low testosterone level in a woman is evidence for need, if 15 or 20 ng/dL she most probably needs testosterone replacement, at 30 to 40 ng/dL she may, at 60 ng/dL or higher a therapeutic trial is safe but should only be conducted if the patient is highly symptomatic;

 Estradiol (1-month peak);

 CBC with differential

 CMP;

 Lipids (statins and other drugs);

 TSH, free T3, and free T4;

 FSH (1-month peak);

 SHBG;

 Iron, ferritin.

Laboratory evaluation should be repeated annually; however unexpected developments should be tested immediately with specific studies (CBC, thyroid, etc.). Patients should be asked to complete questionnaires before starting treatment and then on a regular basis in order to assess and document treatment efficacy. Remember, laboratory studies are much less predictive of need for repeated treatment than symptoms.

Treatment Specifics

You need to think carefully about what dose you should use. For example, you do not want a

woman to have a testosterone level of 1000 ng/dL, but 300-400 ng/dL for a short period of time is not unreasonable. For men, the testosterone level can rise to 1500 ng/dL at the peak and drop back down and that is fine. At this point, I think it is important to dispel the myth that testosterone is a male hormone. A woman's testosterone level is 10-times higher than her estrogen level. In women, you also need to think very carefully about which hormones you should use to treat your patients.
Should you treat with testosterone alone like Greenblatt did? Treating with testosterone alone is associated with less bleeding, cancer reduction, and a lower incidence of breast tenderness (remember, anastrozole can also be given to minimize aromatization). Testosterone alone is appropriate in the following instances:

- Menopausal syndrome in whom estrogen therapy has proved unsatisfactory or is contraindicated;
- In combination with estradiol pellets in patients with uteri who have severe menopausal symptoms, in order to prevent the untoward bleeding induced by estrogens;
- Dysmenorrheic patient with endometriosis or small fibroids;
- Fibomyomata for whom surgery is not feasible;
- Nocturia of endocrine origin;
- Increased libido is desired;
- Palliative measure in patients with advanced carcinoma of the breast;
- In combination with desoxycorticosterone pellets for Addison's disease.

Or should you use testosterone and estradiol? Estradiol and testosterone can be useful for treating persistent hot flashes, insomnia, and vaginal dryness. It is more suitable for women who are thin and with low body fat. Finally, don't forget about progesterone. Progesterone can be very effective at treating insomnia and anxiety, and as an adjunct for the prevention and treatment of tremors or seizures. Progesterone should be cycled, for example at the end of the cycle for 2-weeks from the 12th day to 25th day. Progesterone (50-200 mg) should be administered sublingually in patients who are really jittery and are experiencing severe sleep problems. Oral micronized progesterone capsules are preferable.

Pellet Implantation

Pellet implantation is a simple in-office procedure which takes 10-15 minutes (less with practice). The pellets are placed under the skin in the upper gluteal area. Some people prefer them in their abdominal wall; however, they are typically best tolerated in the upper gluteal area. It is important to tell patients that they do not need to get the pellet removed as it will dissolve completely. Once implanted, pellets will disappear almost universally without any fibrous tissue or any secondary side effects within 4-5 months in men and 3-4 months in women.
Before carrying out pellet implantation the area needs to be anesthetized. Lidocaine with epinephrine plus bicarbonate to 20% is preferable because it does not sting. Furthermore, the epinephrine prevents excessive bleeding. After anesthetizing the area make a 5 mm incision and advance the blunt obturator through the incision at a 45° angle parallel to the skin until it is set at its full depth. Then place the pellets in the cannula and advance. Click the pellets into place, withdraw the trocar, place Steri Strips, and compress. That's it. Your patient is now treated for 3-4 months and there are no issues whatsoever with compliance.

CONCLUDING REMARKS

Bioidentical hormone pellet therapy can transform the life of patients of all ages. As we have learnt pellet therapy provides consistent physiologic levels, 100% compliance, no cross-contamination, and global benefits.

REFERENCES

1. Butenandt A. Über „Progynon“ ein krystallisiertes weibliches Sexualhormon. *Die Naturwissenschaften.* 1929;17:879-879.
2. Butenandt A. Über die chemische Untersuchung der Sexualhormone. *Zeitschrift für Angewandte Chemie*. 1931;44:905.
3. Butenandt A, Hanisch G. Uber die Umwandlung des Dehydroandrosterons in Androstenol-(17)-one-(3) (Testosterone); um Weg zur Darstellung des Testosterons auf Cholesterin (Vorlauf Mitteilung). [The conversion of dehydroandrosterone into androstenol-(17)-one-3 (testosterone); a method for the production of testosterone from cholesterol (preliminary communication)]. *Chemische Berichte* (in German).1935;68:1859–1862.
4. Ruzicka L, Wettstein A. Uber die kristallinische Herstellung des Testikelhormons, Testosteron (Androsten-3-ol-17-ol) [The crystalline production of the testicle hormone, testosterone (Androsten-3-ol-17-ol)]. *Helvetica Chimica Acta* (in German). 1935;18:1264–1275.
5. Greenblatt RB, Suran RR.Indications for hormonal pellets in the therapy of endocrine and gynecic disorders. *Am J Obstet Gynecol.* 1949;57:294-301.

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