



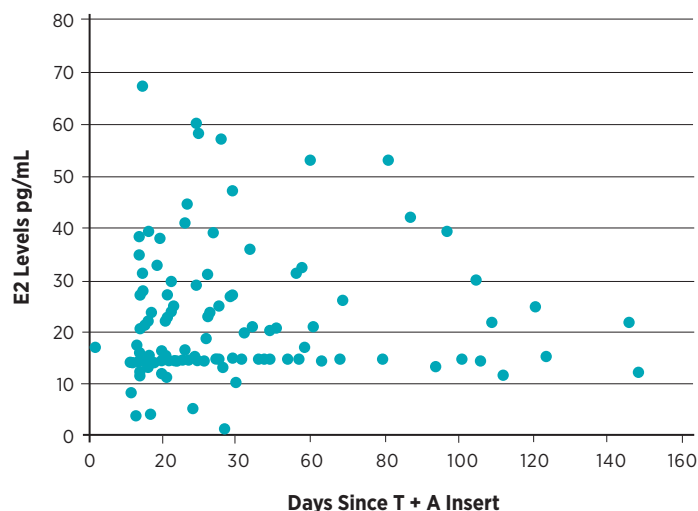
Subcutaneous Testosterone Anastrozole Therapy in Men: Rationale, Dosing, and Levels on Therapy

SUPPLEMENTAL CONTENT

Supplement 1. Efficacy of Subcutaneous Testosterone Anastrozole Implant (T + A)

In early studies (2009 to 2011), 130 male patients were treated with 7 mg to 12 mg of anastrozole in combination with testosterone (mean T dose 1280 mg). The figure below demonstrates estradiol levels over the clinical lifespan of the implant, day 2 through day 149. The mean serum estradiol level was $21.3 \text{ pg/mL} \pm 11.9 \text{ pg/mL}$. Specifically, estradiol levels remained low over the entire lifespan of the T+A implant, confirming continuous delivery and zero-order release identical to T implants. Although some men (22/130) had elevated estradiol levels greater than 30 pg/mL on these lower doses of anastrozole, overall, E2 levels were controlled for the life of the implants, confirming *in vivo* continuous delivery and zero-order release identical with the T implant alone. Over 60% of men on testosterone implants alone had an average serum estradiol level of >30 pg/mL to 50 pg/mL and/or had side effects from testosterone therapy related to estrogen excess including lack of effect from T therapy, fluid retention, edema, bloating, anxiety, irritability, aggression, weight gain, breast pain, or gynecomastia.¹

SERUM ESTRADIOL LEVELS OVER TIME IN MEN TREATED WITH 7 MG TO 12 MG OF SUBCUTANEOUS ANASTROZOLE COMBINED WITH TESTOSTERONE.



Reference

1. Glaser R, Dimitrakakis C. *Subgroups of Patients Treated with an Aromatase Inhibitor (Anastrozole) Delivered Subcutaneously in Combination with Testosterone*. 9th European Congress on Menopause and Andropause. 2012; 424.

EARLY DATA:

Subgroup of 97 patients with E2 levels measured prior to and after first aromatase inhibitor therapy (i.e., first T + A insertion).

RESULTS:

E2 Prior: Mean E2 level on T alone $54.8 \text{ pg/mL} \pm 21.0 \text{ pg/mL}$

E2 After: Mean E2 level after first T + A therapy $21.4 \pm 11.4 \text{ pg/mL}$

There was over a 40% reduction in serum estradiol levels following first T + A therapy.

DATA are available upon request.

Supplement 2. Estimates for Testosterone and Estradiol Levels.

Due to the nature of real life data, laboratory results were available from multiple labs and varying assays. In order to calculate mean and standard deviation values of estradiol levels and T levels reported as less than (<) or greater than (>), estimates were made based on an average of existing data in our patient population for that specific range.

RESULTS:

1. Estradiol reported as less than: <5 (4.3 pg/mL), <10 (5.83 pg/mL), <12 (7.06 pg/mL), <15 (8.78 pg/mL), <20 (11.14 pg/mL), <30 (14.51 pg/mL)
 2. T reported as greater than: >1400 (1543 ng/dl), >1500 (1665 ng/dl), >1600 (1702 ng/dl)
- DATA are available upon request.

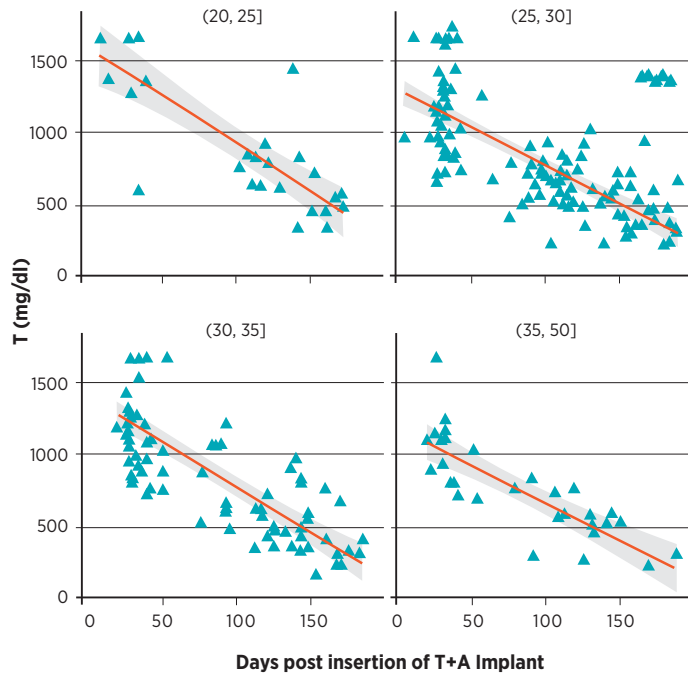
Supplement 3. Hormone Levels Over Time Separated by Body Mass Index: 20-<25, 25-<30, 30-<35, 35-50.

KEY POINTS:

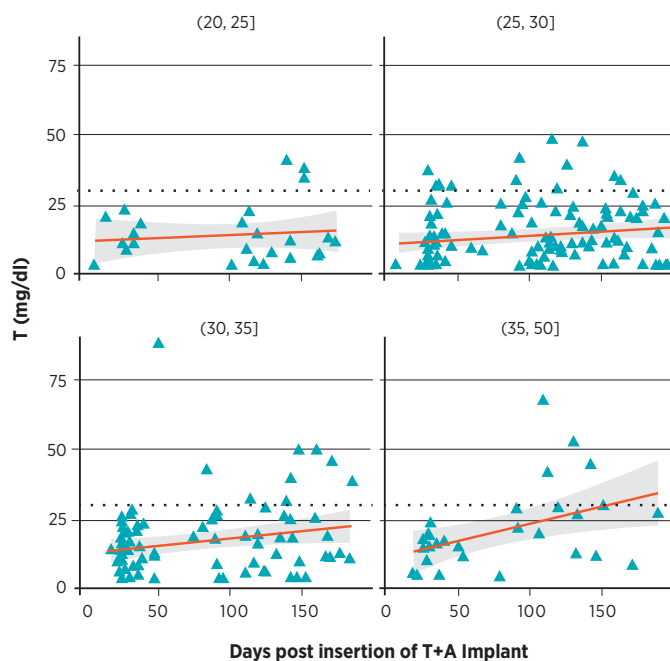
- Note the difference in T levels throughout the cycle between the lowest Body Mass Index (BMI) (<25) and the highest BMI (>35). T levels remain significantly higher throughout the cycle in patients

FIGURE 1.

TESTOSTERONE LEVELS OVER TIME SEPARATED BY BMI. VARIATION IN INTERCEPTS WITH NO DIFFERENCE IN SLOPES.

**FIGURE 2.**

ESTRADIOL LEVELS OVER TIME SEPARATED BY BMI. ESTRADIOL INCREASES AT A GREATER RATE FOR MEN WITH THE HIGHEST BMI.



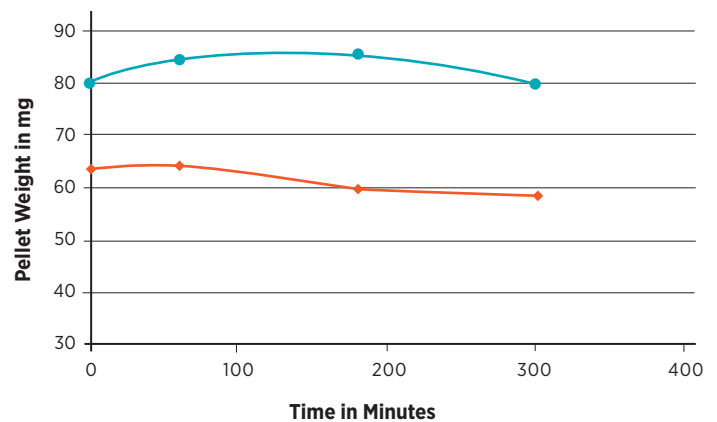
with a lower BMI compared to a higher BMI despite lower dosing (FIGURE 1).

- T levels decline at about 0.7% to 0.8% per day in all BMI groups with no difference in the slope between BMIs.
- Estradiol increases at about 0.25% per day but remains low in all BMIs.
- Estradiol increases at a greater rate (slope) in men with the highest BMI, with a level of difference significant at 0.1, $P=0.09$ (FIGURE 2).
- The intercepts for T vary by BMI but not for estradiol.
- The intercept for BMI <25 is 1604 ng/dl compared to about 1200 for BMI >35.

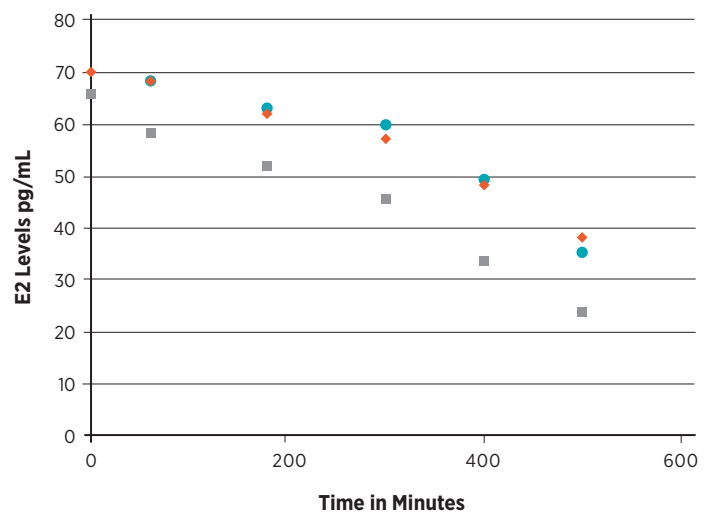
Supplement 4. Heat Accelerated Dissolution in Oil.

DISSOLUTION OF LETROZOLE AND LETROZOLE + STEARIC ACID IN OIL.

HEAT ACCELERATED DISSOLUTION IN OIL



HEAT ACCELERATED DISSOLUTION IN OIL



Note the difference in the dissolution rate between the autoclaved implant and the non-autoclaved implant.

WEIGHT (MG) OVER TIME:

TIME (MINUTES)	T + A (AUTOCLAVED) MG	T + A (NON-AUTOCLAVED) MG
0	69	67
60	68	59
180	63	53
300	60	46
400	49	34
500	35	24

PERCENT ORIGINAL PELLET WEIGHT OVER TIME:

TIME (MINUTES)	T + A (AUTOCLAVED) MG	T + A (NON-AUTOCLAVED) MG
0	100.0	100.0
60	98.5	88.0
180	91.3	79.1
300	87.0	68.6
400	71.0	50.7
500	50.1	35.8

PERCENT DIFFERENCE IN DISSOLUTION OVER TIME:

TIME (MINUTES)	DIFFERENCE IN % DISSOLUTION
0	00.0
60	11.0
180	13.4
300	21.1
400	28.5
500	28.6

Note the increase in difference over time.