

TESTOSTERONE IMPLANT DOSING WOMEN

Serum testosterone ranges are based on *endogenous* hormone production. There is no evidence to support that dosing for exogenous testosterone therapy should be based on establish ranges from endogenous production (which have been shown to be inaccurate in women and children). Subcutaneous testosterone doses from 75 mg to 150 mg (and up to 225 mg) have been shown to be efficacious without significant adverse effects.

Testosterone implants have been used in women for 70 years (1938-2008). Doses used in published studies range from 50 up to 225 mg. Common doses currently used in the United States are 75, 100, 112.5 mg, 125 and 150 mg. There are minimal side effects at these doses (slight increase in facial hair and rarely, mild acne), which may be reduced by lowering the dose, if the patient chooses. If measured, **serum** treatment levels are elevated above non-treatment (endogenous) levels at month one (Thom 81, Burger 84, Brincat 84, Gambrell 06, Glaser unpublished 2007). Serum testosterone levels on pellet therapy may measure over 3 times higher than upper normal endogenous levels, There are no serious side effects at these levels, a slight increase in facial hair in a minority of patients (Brincat 84).

Despite elevated **serum** levels with ‘adequate’ testosterone therapy, urine, saliva and breast milk levels remain normal. There are no clinical signs of androgen excess at these treatment levels. Symptoms return when testosterone levels reach the upper end of non-treatment ranges for premenopausal females (Burger 84, Brincat 84, Glaser 07). End organ response to testosterone therapy remains optimal at doses of **100 mg or higher** (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.). On average, testosterone implants last between 3 and 4 months in female patients. **Individual** treatment doses, therapeutic threshold and treatment ranges are established and are reproducible.

Blood concentrations of implant hormones are increased and there appears to be an *individual* threshold blood level below which a response is not observed.

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 effects (slight increase in facial hair and acne). The most common dose was 100 mg.

The addition of testosterone, delivered by pellet implant, was shown to reduce the incidence of breast cancer in women treated with conventional hormone therapy.

DOSING CONSIDERATIONS/DATA

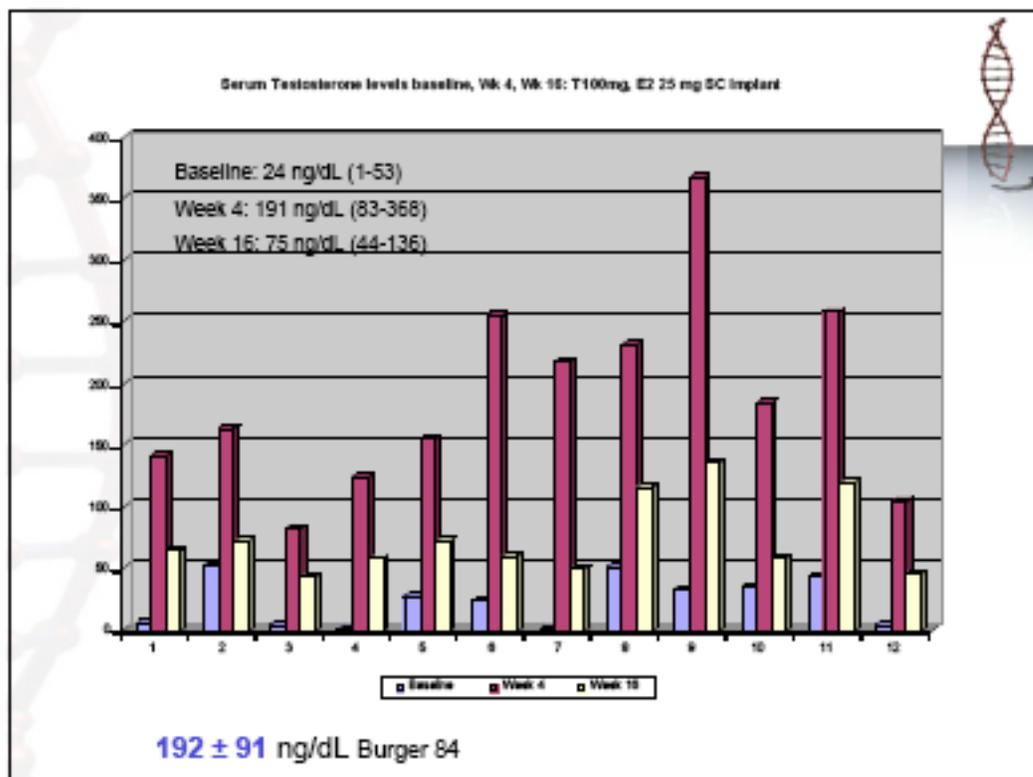
Dosing may be adjusted based on clinical symptoms and side effects. Serum levels are **not** suggested as a means of monitoring therapy as they can vary significantly throughout the day and between patients. A single serum testosterone level is not reflective of clinical end organ response. Serum treatment levels are not 'sin e qui none' with end organ response. Serum levels are transient pictures of a dynamic equilibrium. Senescence may be related to end organ androgen resistance or insensitivity, similar to 'insulin resistance'. Higher levels of hormones in serum (insulin) are needed to produce the desired effect at the end organ (glucose levels).

Serum testosterone 'ranges' are based on **endogenous** hormone production. If therapy is based on endogenous hormone level ranges, the patient will remain under-treated. There is **no data** to support the recommendation 'that serum levels of testosterone with therapy should remain within normal endogenous ranges'. Data exists to the contrary. In a study (Choi 06, JCEM) that looked at the effects of testosterone replacement in human immunodeficiency virus infected women with weight loss, testosterone kept within the upper limits of **normal ranges**, **failed to** increase/improve strength, muscle mass, lean body mass, body performance, quality of life or cognitive function.

There are no reported serious adverse drug events with testosterone pellet therapy, despite treatment serum treatment ranges consistently above endogenous ranges in women. There is no data to support that 'above normal' serum levels from exogenous therapy, correlate with any serious side effects. Higher levels of serum testosterone, during therapy, do correlate with clinical response. In both men and women, end organ sensitivity (i.e. AR gene sensitivity, Crabbe 07) is an individual factor, which affects dosing required and response to therapy. This may explain the large inter-individual variation in free testosterone levels and end organ effect. Androgen sensitivity declines with age and higher serum levels may be required to maintain optimum physical and mental health. Even in men treated with pellet implant, symptoms are controlled with higher serum levels of testosterone: peaking at 1100ng/dL and maintained above 600 ng/dL. Depending on AR sensitivity, some men require lower dosing.

Historical studies **have** demonstrated that serum levels, during exogenous testosterone therapy delivered by implant, above endogenous baseline levels are NOT associated with serious adverse effects or symptoms of excess. Even doses of over 500-600 mg up to 1800 mg used to treat metastatic breast cancer survivors have had no serious adverse effects. The desired end point for monitoring 'adequate' therapy, deepening of the voice (>500 mg dose) and masculinization (1800 mg dose) were reversible as the pellets wore off.

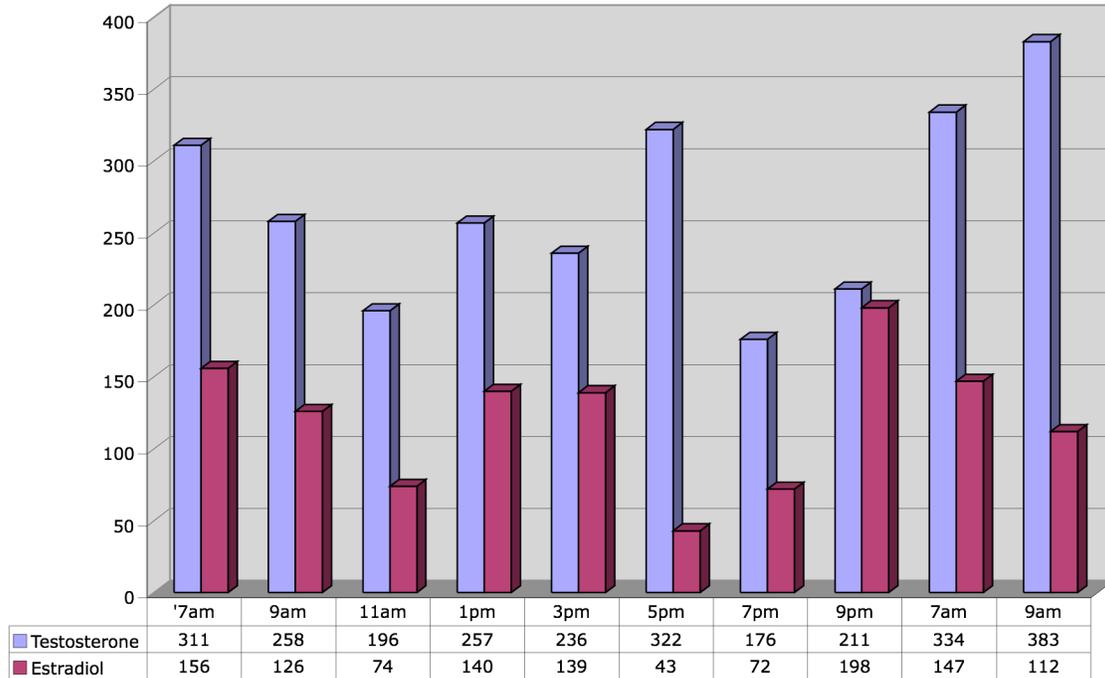
Serum testosterone measurements are variable, inconsistent, and inaccurate, show extreme intra, and inter individual variation.



Individual variation at week 4 is shown above with 100 mg pellet implant (Data from Glaser 07). The range of testosterone measured by RIA was 83-368 ng/dL (4.4 fold difference, identical dose). **None of the 12 patients had any symptoms of testosterone excess.** The average (191 ng/dL) correlates with what Burger published in 1984 (192 ± 91 ng/dL). Symptoms return when testosterone reaches the upper limits of normal (70 ng/dL), even higher in some individuals. Again, no symptoms of testosterone excess are reported.

In addition, serum/blood hormone levels vary *significantly throughout the day*, both endogenous and with pellet therapy. The significance of a single measurement is questionable.

26 h Venous Bld Spot Testosterone and Estradiol (T112.5, E2 50)



The above graph shows diurnal testosterone variation throughout the day **by over 200 ng/dL** by **venous bloodspot** (which may measure levels higher than serum, 2-3 fold baseline and 40% higher with T implant therapy). There were no signs or symptoms of androgen excess.

The significance of a single serum measurement remains unanswered. There is no evidence that therapy should be based on a single measurement.

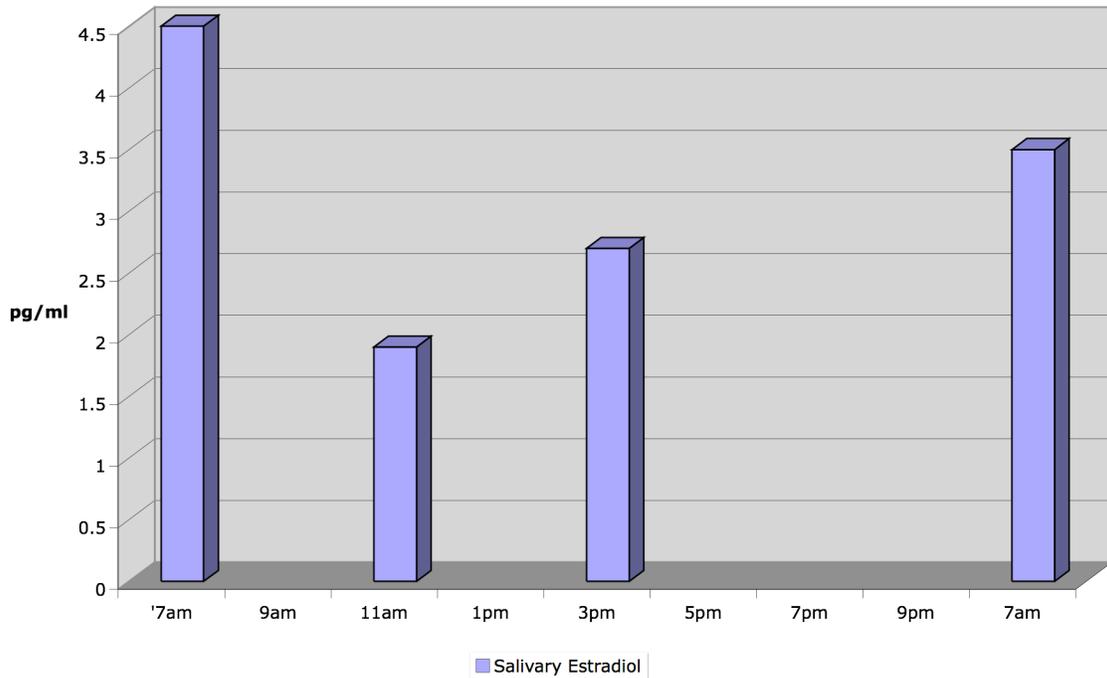
In this same patient, salivary and 24- hour urine levels remained within normal limits. Salivary estradiol and testosterone levels also exhibit diurnal variation. Despite elevated testosterone levels measured in blood, testosterone metabolites in 24-hour urine remained in the lower half of normal (estradiol, in the lower 20'th percentile).

24-Hour Urine (T 112.5 mg, E2 50 mg)

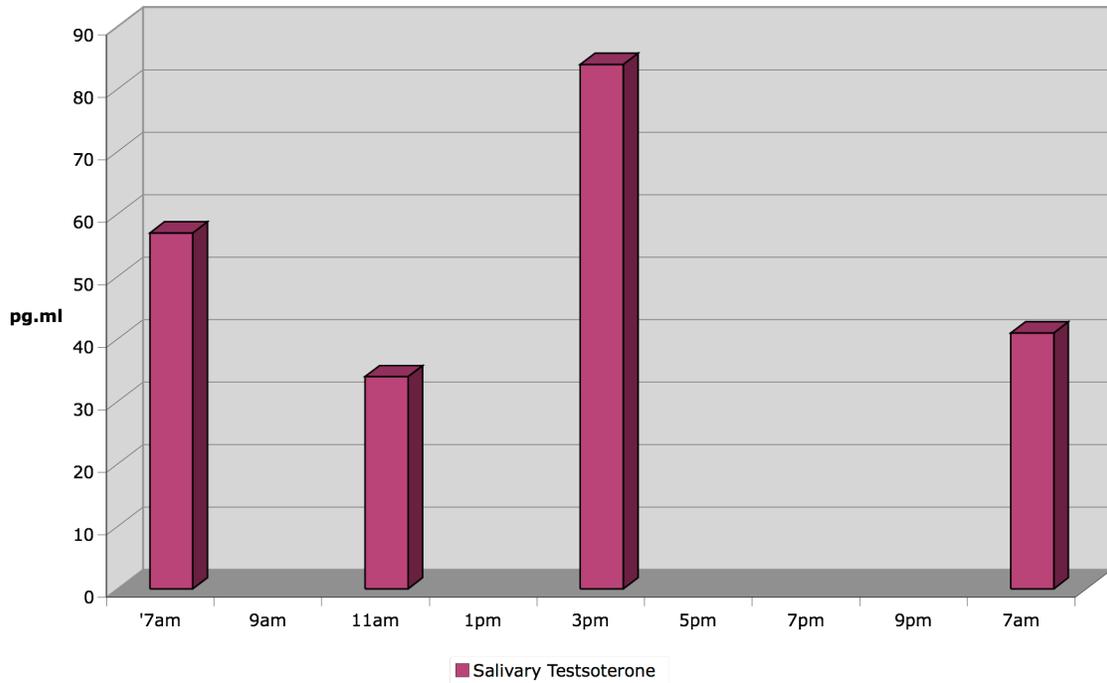
Estradiol 7.4 ug (1-45)

Testosterone 16.5 ug (5-35)

24 h Salivary Estradiol (E2 Implant 50 mg)

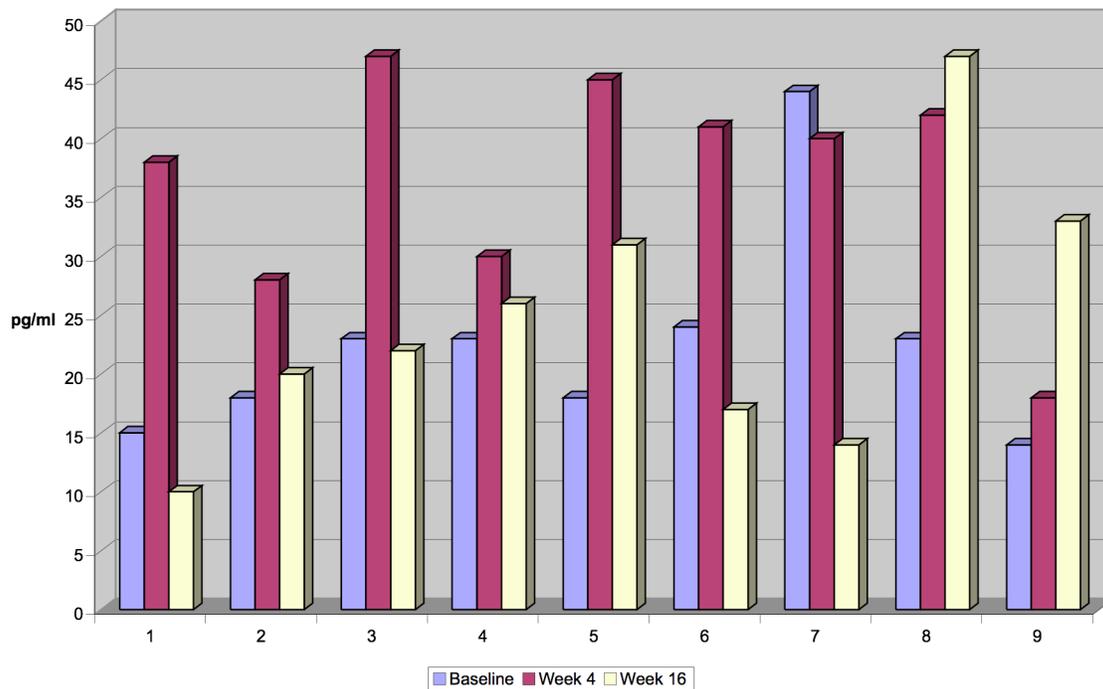


24 h Salivary Testosterone Levels (T implant 112.5 mg)



Salivary testosterone levels in patients with a 100 mg implant also remained within normal limits in 11 of 12 patients at week 4 (20-50 pg/mL), despite elevated serum levels (3 baselines levels inadvertently discarded).

Salivary testosterone levels: T 100 mg SQ implant



**HISTORICAL DOSING TESTOSTERONE PELLET IMPLANTS
RELIEF OF SYMPTOMS: END ORGAN RESPONSE
NO SERIOUS ADVERSE SIDE EFFECTS**

- Greenblatt 1949
 - Dose: 75, 150, 225 mg (1-3, 75 mg testosterone pellet implants)
 - Indications
 - Menopausal syndrome
 - Prevent uterine bleeding caused by estrogens
 - Dysmenorrheic patients with endometriosis or small fibroids
 - Fibromyomata
 - Nocturia
 - Increased libido desired
 - Palliative measure; carcinoma of the breast
 - Addison's disease (Adrenal fatigue)
- Jones 2004
 - Dose 50-150 mg, most common 100 mg
 - Reduced the incidence of breast cancer
 - Increased bone density
 - Memory and concentration
 - Sex drive, libido
 - Strength
- Gambrell/Natrajan 2006
 - Dose 75, 150 (most common), 225 mg
 - To treat symptoms of T deficiency

- No increase in the incidence of breast cancer with estradiol (E2) 50-75mg implant (with T)
- No adverse affects on lipids or lipoproteins
- Mean serum T levels **80-262** ng/dL
- Implanted 3-6 m up to 29 y fu
- Natrajan 2002
 - Dose T: 75, 150 (most common), 225 mg
 - No increase in recurrence of breast cancer (with or without estrogen therapy)
- Tutera (Submitted for publication)
 - T dose: 75-225 mg
 - 967 women treated for 10 years
 - 1 case of breast cancer at year 2
- Burger 1984
 - Dose 100 mg
 - Levels peaked at one month 101-**283 ng/dL** and declined by month 5 (38-106 ng/dL; average **71.4 ng/dL**) at which time symptoms returned and pellets were reinserted
 - Treatment testosterone levels **three times normal** of un-supplemented ranges.
 - No symptoms of testosterone excess
 - No change in lipid profile
 - One patients with mild increase in facial hair
 - Symptoms improved
 - Libido
 - Sexual satisfaction
 - Fatigue
 - Memory/concentration
- Thom 1981
 - Dose: 100 mg, 200 mg.
 - T levels mo.1 100 mg 143 ng/dL (range 60-171 ng/dL)
 - T levels mo.1 200 mg 174 ng/dL (range 148-326 ng/dL)
 - No change in FSH, did increase E2 (not ss)
 - Variation in levels between patients serum levels
 - Peaked at month 2
 - Symptoms are do to change in levels NOT absolute low levels
 - 100 mg worked as well as 200 mg for libido
- Brincat 1984
 - Dose: T 100 mg
 - Indications
 - Lethargy
 - Depression
 - Loss of libido
- Brincat 1987
 - Dose: T 100 (with E2 50)
 - Increase collagen
- Cardoza 1984
 - Dose: T 100 mg
 - Symptoms relieved (with E2 50)
 - Headache, insomnia, hot flushes, bone pain, palpitations, dyparenia, libido, irritability, memory, concentration, depression, lethargy, urethral syndrome

- Re-implant as early as 3 months (3-12)
 - Acne 2%, Increase facial hair 20%
 - No other symptoms of excess T
 - Return of Symptoms when levels in *upper normal range*
- Barlow 1986
 - Dose: T 100 mg (with E2 50)
 - T plus E2 gained bmd (E2 alone maintained)
 - No change in BP, LFT's
- Montgomery 1987
 - Dose: T 100 mg (E2 50)
 - Improved: anxiety, somatic disturbances, Depression
- Dow 1983
 - Dose: T 100 (E2 50)
 - Psychological complaints, somatic complaints, vasomotor sx's, libido, response, dyspareunia
- Studd 1990
 - Dose Testosterone 100mg (with E2 75)
 - Increased bone density
- Garnett 1991
 - Dose: Testosterone 100 mg q 6 mos. (with E2 50-75) up to 24 years (mean 5.2y)
 - Dose thought to be insignificant for bone density
 - Testosterone levels at re-implantation .91-1.51 nmol/L 11.4-169 ng/dL
 - Indications
 - Libido
 - Mood
 - Depression
- Saavas 1992
 - Dose T 100 (with E2 75) increased bmd
- Davis 1995
 - Dose T 50 mg (with E 50)
 - Increased bmd and sexuality
- Davis 2000
 - Dose T 50 (E2 50)
- Seed 2000
 - Dose T 50 (with E2 50)
 - T did not attenuate benefits of E2 on LDL TG
- Sands 1997
 - Dose T 100 (E2 50)
 - Testosterone did not attenuate the benefits of E2 on lipid or carbohydrate metabolism
- Worboys 2000
 - Dose T 50
 - Improved blood flow, brachial artery vaso-dilation
- Loeser 1941
 - T implants to treat breast cancer
 - Prevented recurrence
 - Improvement/control in metastatic disease
 - Dose **500-700 mg** implant. Most common 600 mg (every 6 months)
 - Symptoms of excess (hoarse voice, enlarged clitoris, increased hair)
 - **Symptoms 'faded' at 6 months**

- Re-implantation at return of mets then every 6 months
 - Only hoarse voice remained/continued with q 6 month implantation
- Dose **1500-1850 mg** in metastatic disease
 - ‘Obvious improved health’ from bedridden state
 - Decreased pain
 - **Temporary** masculinization (desired endpoint)
 - Repeat dose when disappears
- Conclusion: Implant at the time of surgery may prevent recurrent disease

After treating over 900 patient in clinical practice

Testosterone Pellet Dosing:

- 100mg (30%)
- 110-112.5 mg (29%)
- 125 mg (23%)
- 150 mg (15%)
- 50, 75 mg (3%)

Other than slight increase in facial hair (which over 80% of women have and treat prior to therapy) and rare acne (<2%) which often resolves spontaneous or with lowering the dose and eliminated processed carbohydrates (sugar) there were no other side effects of therapy other than edema in the summer in one female patient (history of edema in the past), which resolved with HCTZ. No reports of deepening of the voice were noted. Rare increased sensitivity (<1%) of the clitoris is reported and spontaneously resolves.

The above doses relieve symptoms for an average of 3.5 months (10 weeks to 5 months).

Symptoms shown to be relieved at Testosterone doses of 100, 112.5, 125, and 150 mg:

- Hot flashes, sweating
- Heart discomfort, racing
- Insomnia, sleep problems
- Depressive mood, mood swings
- Irritability, nervous
- Anxiety
- Physical and mental exhaustion
- Impaired memory, decreased concentration, forgetfulness
- Sexual problems, decreased libido and satisfaction
- Bladder incontinence, dysuria, frequency, urgency
- Vaginal dryness, burning
- Joint and muscular pain
- Bone loss, muscle loss, increased fatty tissue

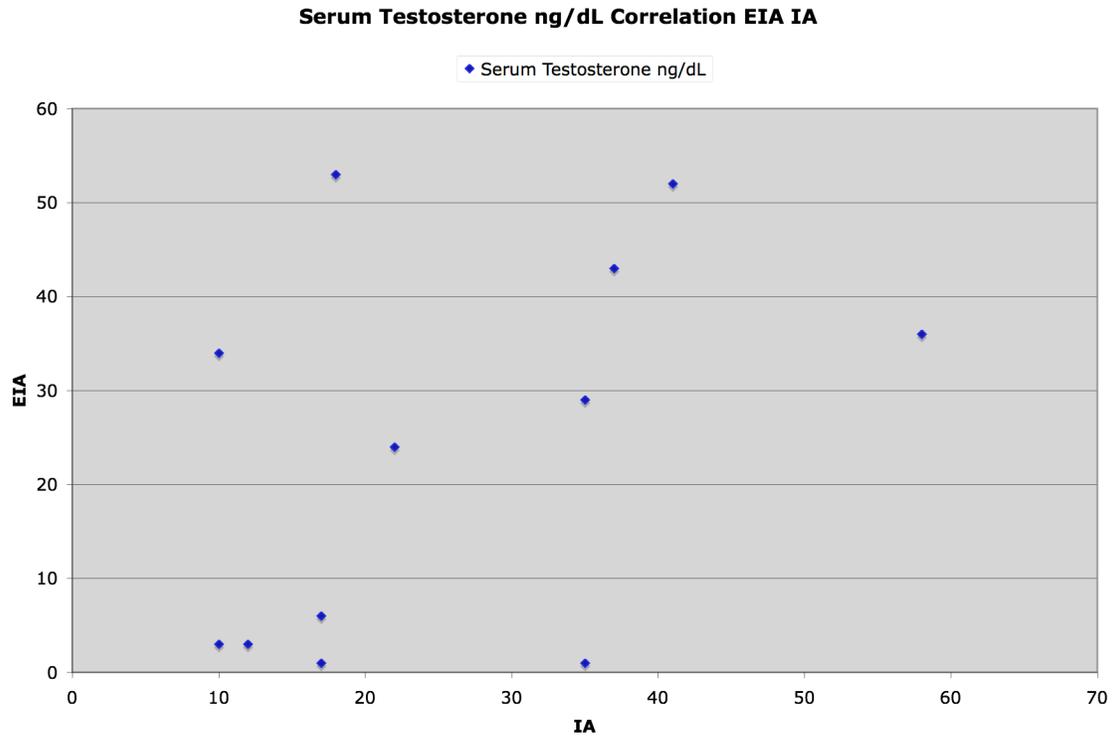
Historical availability of manufactured Testosterone Implants

- England: Organon 100 mg
- US: Bartor Pharmacal 75 mg

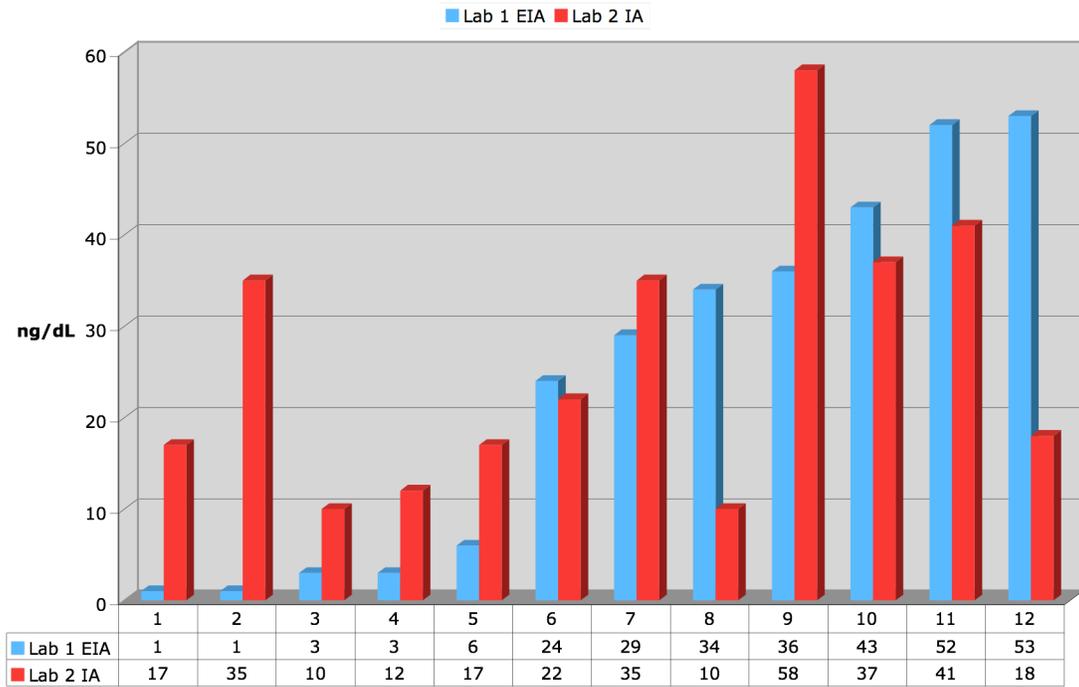
BASELINE MEASUREMENT OF TESTOSTERONE BY IMMUNOASSAY IS INACCURATE IN FEMALES

Measurement of testosterone levels is inaccurate in women. Also, levels vary significantly throughout the day. Routine testing may be misleading. There is no evidence to support that testosterone therapy should be based on a single serum value.

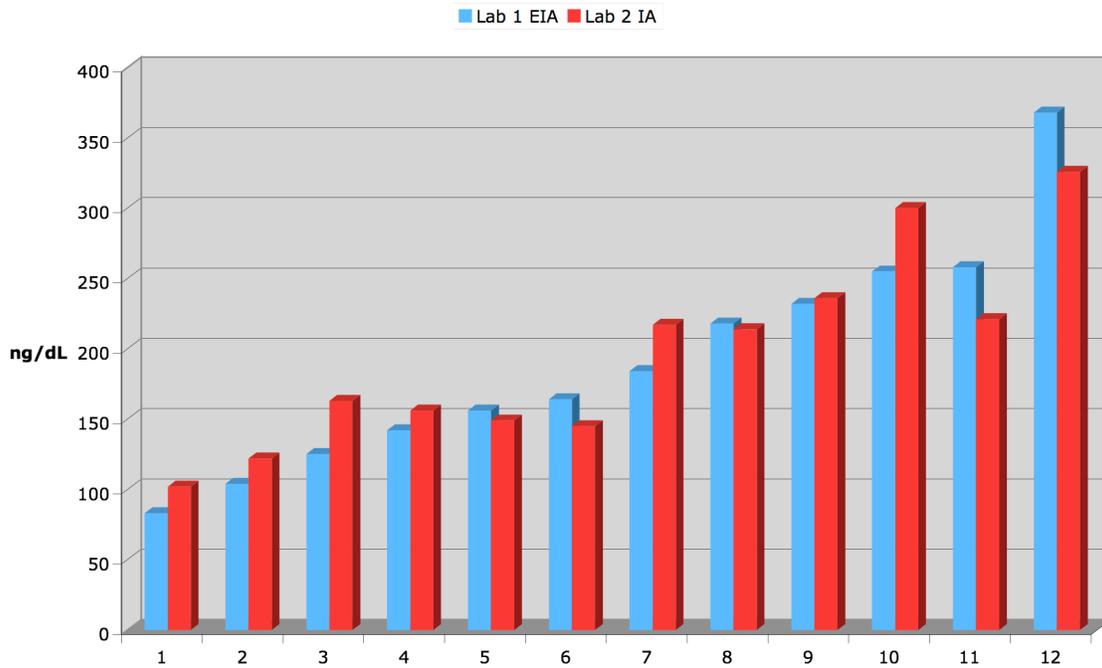
There is **no correlation** between testosterone levels measured at two different labs on the same serum sample from 12 patients, both by immunoassay.



Baseline Testosterone Levels 12 symptomatic post menopausal women

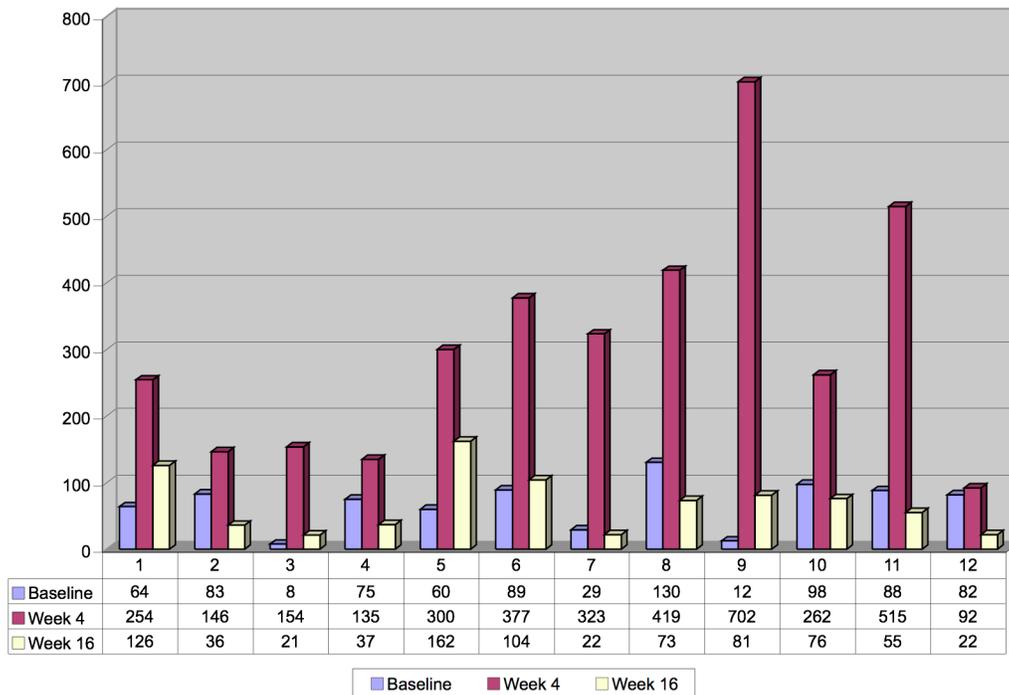


Serum testosterone levles month 1, 100 mg T implant



There is **correlation** between immunoassays at higher ranges, on therapy.

Capillary Bloodspot Testosterone baseline, Wk 4, Wk 16: T100, E2 25 mg SC Implant



Significant variation in capillary bloodspot.

Despite elevated capillary bloodspot levels, which are more variable and higher than serum, only one of twelve patients had elevated salivary testosterone levels at month one (smoker).

In conclusion, historical data supports that exogenous testosterone therapy, by pellet implant should be based on clinical response not on serum testosterone ranges based on endogenous production. Clinical guidelines should be based on available clinical data.

Under-treatment of patients can result in progression of adverse serious health problems do to testosterone deficiency (depression, bone loss, muscle weakness, fatigue, pain, memory loss, incontinence etc.).