Introduction to Bioidentical Hormone Replacement Therapy

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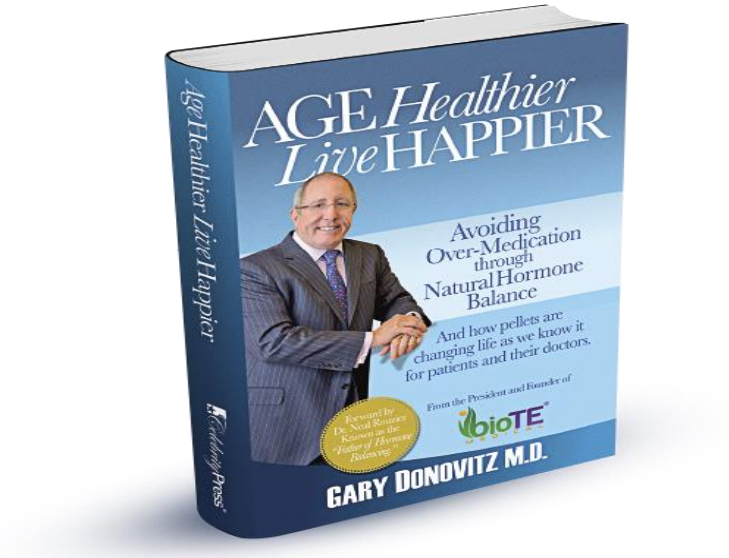
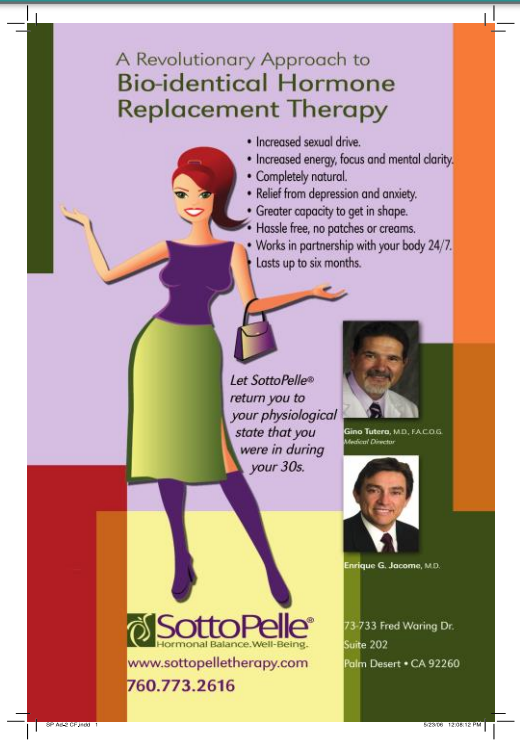
Pellet Therapy Pioneers in the USA





J Am Assoc Gynecol Laparosc. 1999 Feb;6(1):39-44.

Laparoscopic Burch urethropexy in a private clinical practice.

Jacome EG[1], Tutera G, Mattox FT.

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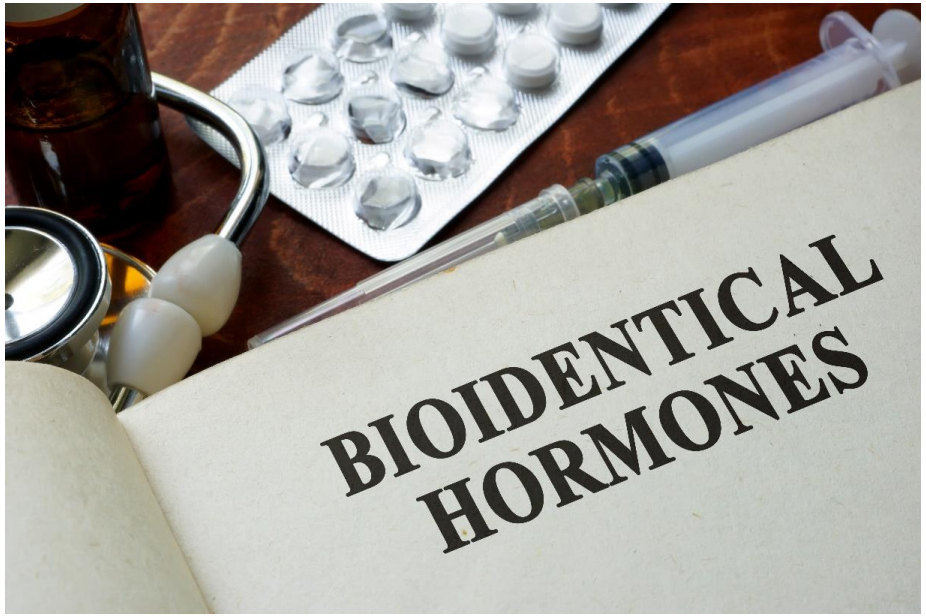
BHRT



1820 US Pharmacopeia was established

- To standardize formulas and dosing forms

Pharmaceutical companies Drawbacks

- Limited dosing options
- Slow response to Emergencies

Bioidentical is defined as a compound having the same chemical and molecular structure as hormones in the human body

- Any modification in the compounding process can create changes in the drug structure; this is a “biosimilar”

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Menopausal Hormone Therapy

Conventional	Compounded
Chemically identical to some human hormones	Chemically identical to human hormones
US FDA oversight	US FDA oversight - Both 503B & 503A
Published scientific research - Plenty	Published scientific research - Increasing
Doses exactly reproducible	Doses flexible based on need
Proven efficacy for indicated use	Growing volume of clinical validation for hormone optimization

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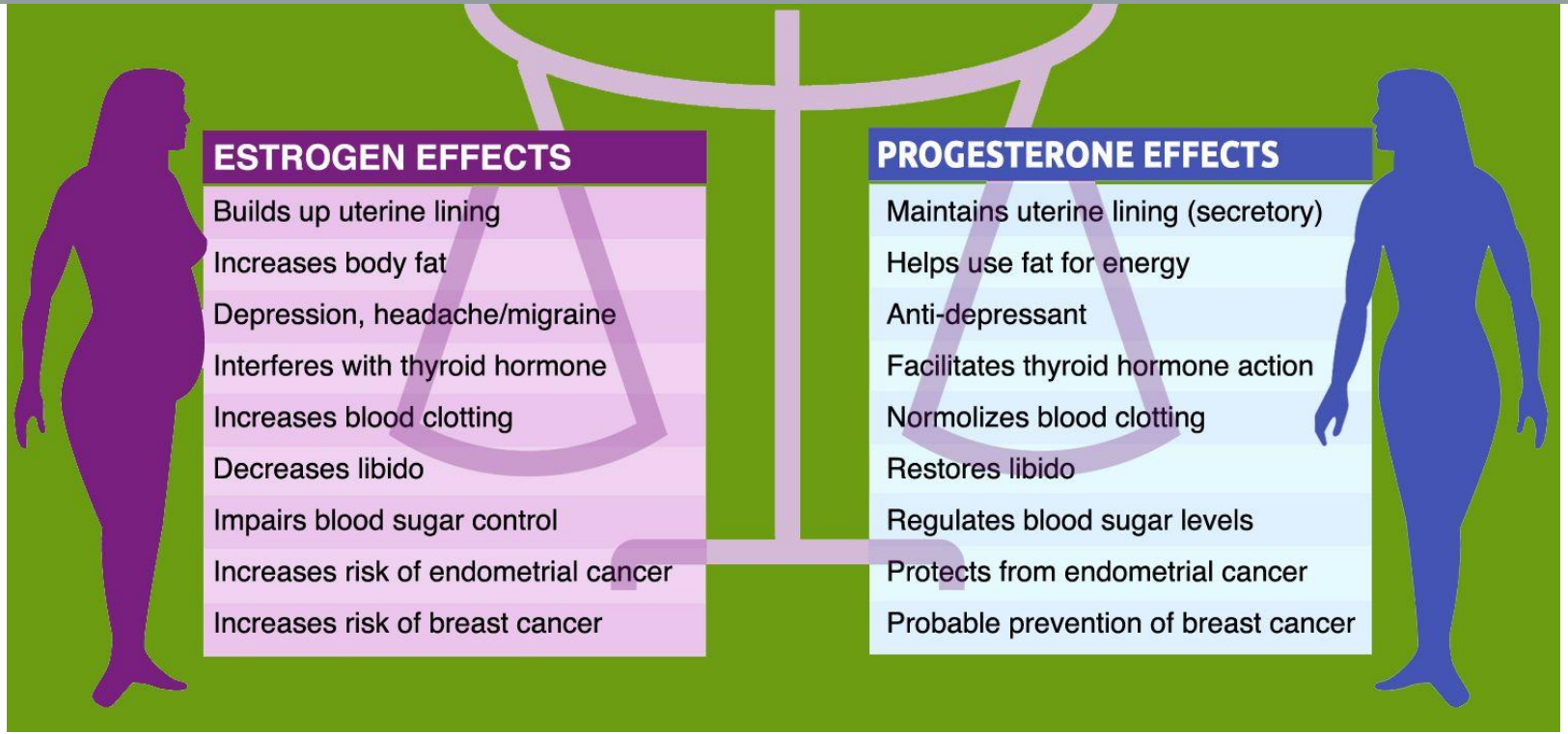
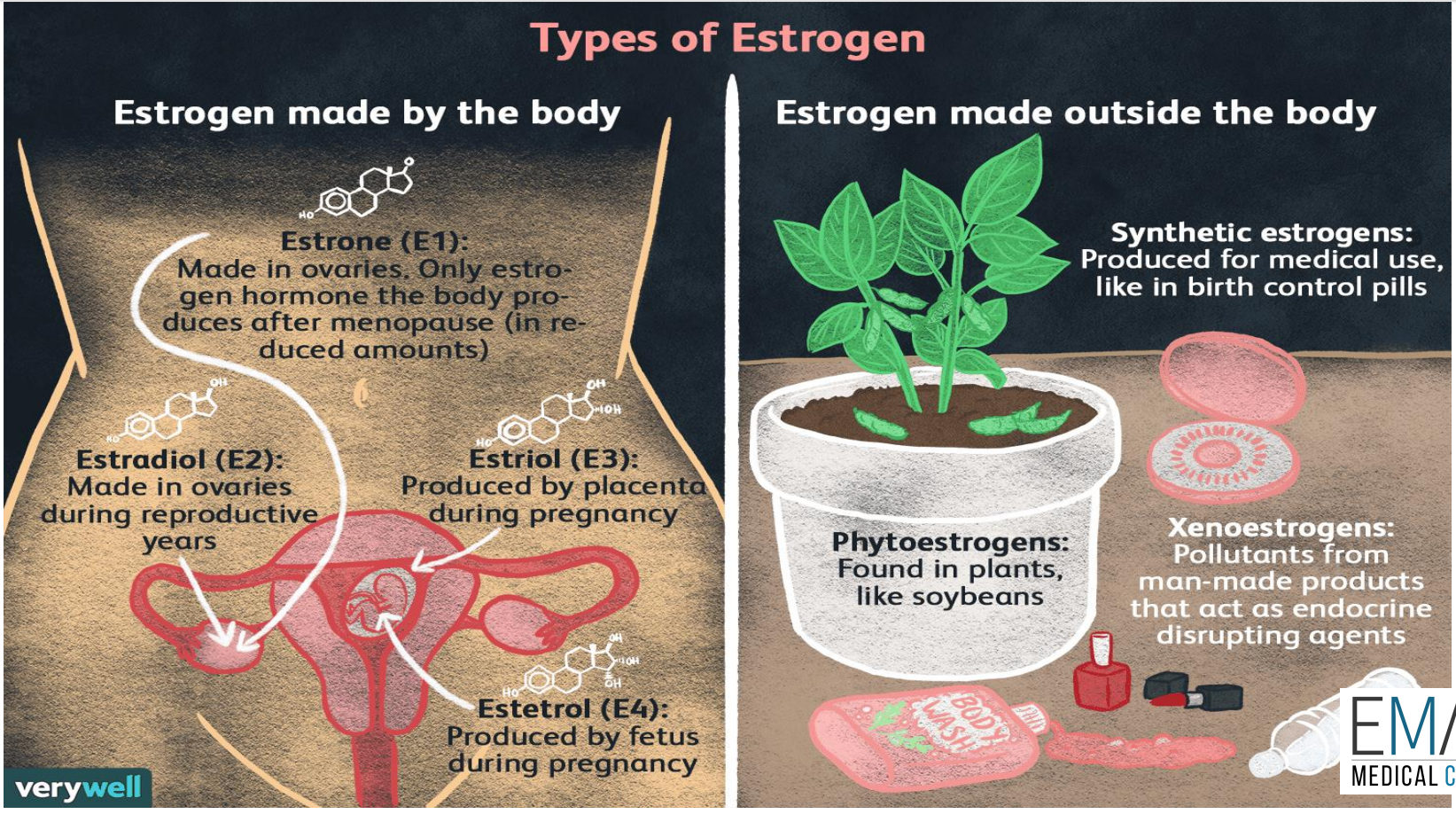
Role of Estrogen and Progesterone



Types of Estrogen



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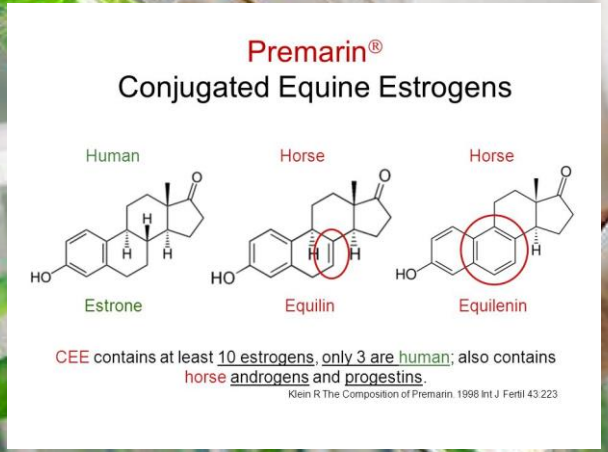
Estrogen

BIOIDENTICAL

- 17-beta estradiol
  - Oral –Estrace
  - Patch – Vivelle, Climara, Alora, Fempatch, Menostar
  - Gel – Estraderm, Estrogel, Divigel, Elestrin
  - Emulsion – Estrasorb
  - Spray – Evamist
  - Vaginal Cream – Estrace vaginal
  - Ring – Estring
- Estradiol acetate
  - Oral – Femtrace
  - Vaginal ring – Femring
- Estradiol hemihydrate
  - Vaginal – Vagifem
- Estropipate Ortho E

NON-BIOIDENTICAL

- Conjugated Equine estrogen (CEE) Premarin
- Equilin sulfate native to horses and estrone sulfate

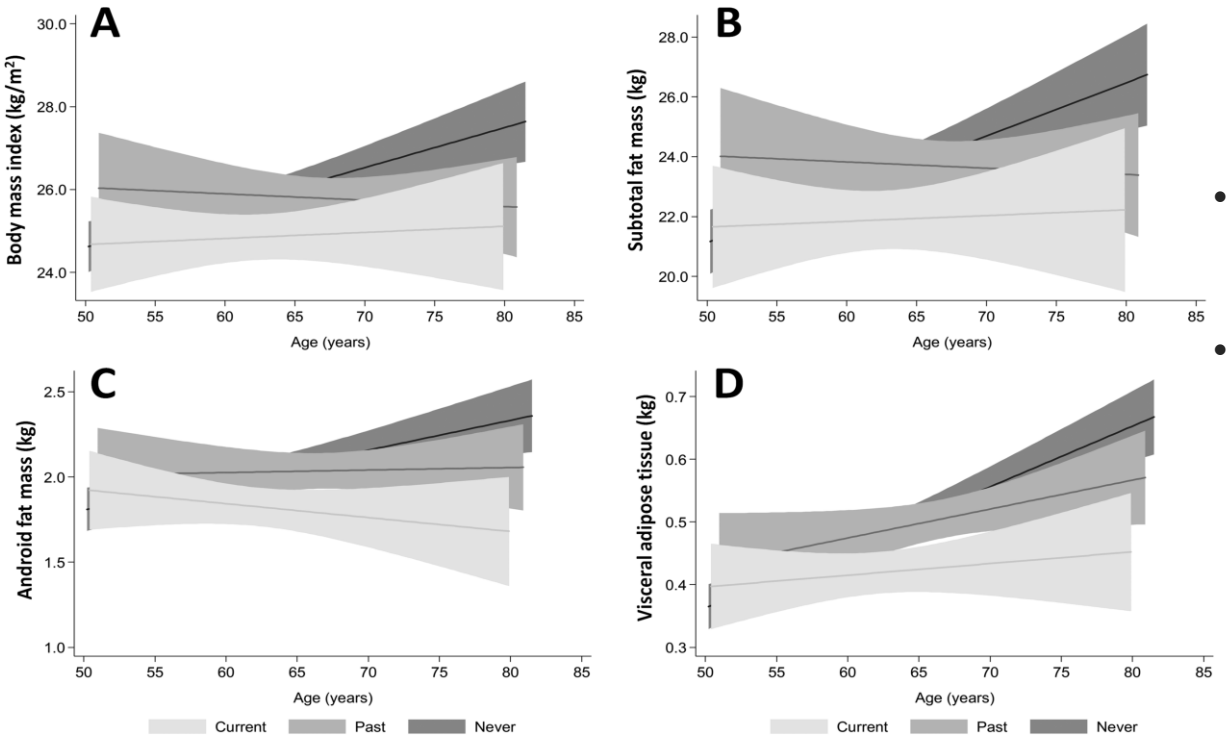


Pattimakiel, L., & Tacker, H. (2011). Bioidentical hormone therapy: Clarifying the misconceptions. *Cleveland Clinic Journal of Medicine, 78*(12), 829-836
Chart from www:menopause.org with permission of North American Menopause Society

Oral vs Transdermal Estrogen

	Oral Estrogen	Transdermal Estrogen
Pharmacokinetics	Serum level peaks and troughs	Serum level remains relatively constant
Inflammatory markers (CRP)	Increased synthesis	Neutral
Lipid effects	Increased triglycerides Increased HDL, Decreased LDL	Decreased triglycerides, Neutral effects HDL / LDL
Blood Pressure	Increased	Decreased
Insulin-like growth factor I	Decreased (may decrease lean body mass and increased body fat)	Neutral
Sex hormone binding globulin	Strongly increased	Minimally increased
Clotting protein synthesis (hepatic enzyme induced)	Increased (may increase risk of VTE)	Neutral (no VTE risk at low doses)

Effect of Menopausal Hormone Therapy on Visceral Adiposity



- Association between hormone therapy, and body fat
- Most studies show reduction in central fat with HRT reduced waist, reduced trunk fat, and decreased visceral fat

Papadakis, G. et al (2018). Menopausal hormone therapy is associated with reduced total and visceral adiposity: The OsteoLaus Cohort.. The Journal of Clinical Endocrinology & Metabolism 103(5). 1948-1957

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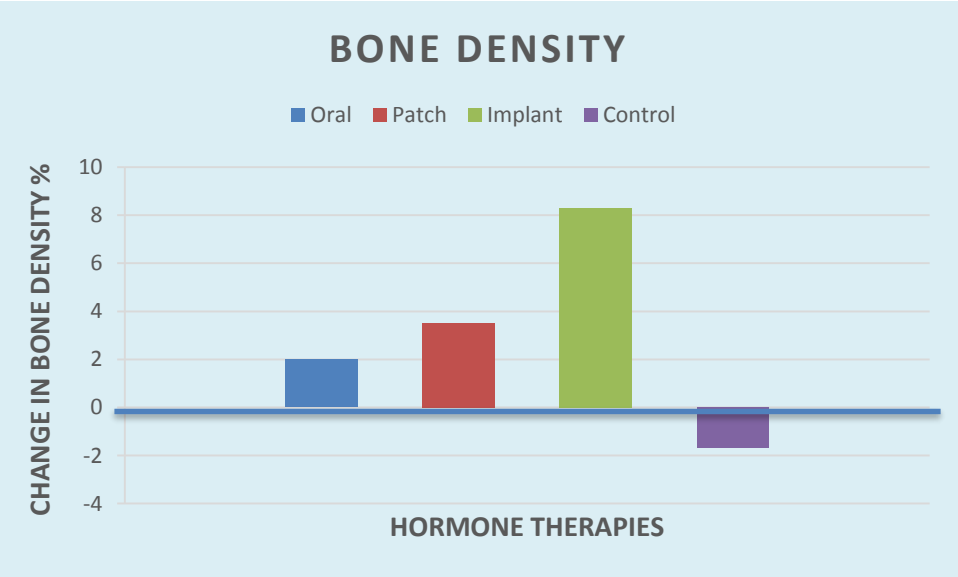
Effect of Estrogen on Bone Density



- Graph shows increase in bone density achieved per year with different routes of estrogen administration
- Study used:
  - Implant 75mg (8.3%)
  - Patch 50mcg (3.5%)
  - Oral Estradiol 2mg (1-2%)

Smith, R., Studd, J. (1993) Recent advances in hormone replacement therapy. *British Journal of Hospital Medicine49*(11), 799-807.

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Pharmacokinetics

Progesterone: Pharmacokinetics

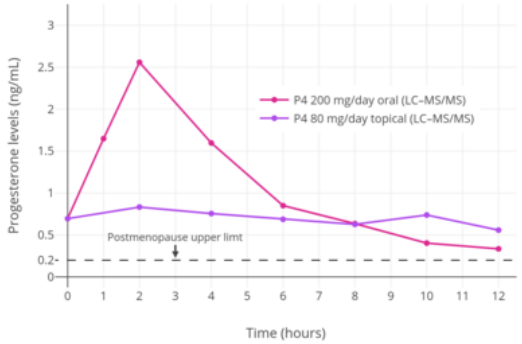
Pharmacokinetic Parameters	Profile
Absorption	• Inactive orally, high first pass metabolism in liver • Injected intramuscularly as oily preparation • Micronized formulation for oral administration; absorption through lymphatics
Distribution	• Short half life (5-7 mins)
Metabolism	• Converted to Pregnanediol in liver • Phase I reaction: Conjugation with glucuronic acid • Phase II reaction: sulfation
Excretion	• Excreted in urine
• Effects lasts longer than the hormone itself • Synthetic Progestins: orally active, metabolized slowly; longer half life	

Pharmacokinetics of Progesterone

Table 5 Pharmacokinetics of progesterone determined by means of liquid chromatography–mass spectrometry (LC–MS) method or radioimmunoassay (RIA) after vaginal and oral administration in postmenopausal women (modified from Levine & Watson[93])

	Vaginal gel 90 mg progesterone		*Oral capsule 100 mg progesterone*	
	LC–MS	*RIA*	*LC–MS*	*RIA*
C_{max} (ng/ml)	10.5 ± 0.5	10.5	2.2 ± 3.1	19.4 ± 12.6
t_{max} (h)	7.7 ± 3.7	7.7	1.0 ± 0.4	1.0 ± 0.4
AUC_{0-24} (ng·h/ml)	133.3 ± 14.6		3.5 ± 5.2	

Pharmacokinetic studies indicate that plasma progesterone levels within the luteal range are achieved with peak levels (mean 77.3 nmol/L= 24 ng/ml) at 2-4 hours following oral administration to postmenopausal women of PROMETRIUM® 200 mg.



Progesterone levels measured via LC-MS/MS during treatment with 200 mg/day oral progesterone or over-the-counter 80 mg/day topical progesterone cream (Pro-Gest) in postmenopausal women.

It is generally accepted that progesterone levels of 5 ng/mL are necessary to inhibit mitosis and induce secretory changes in the endometrium

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Bioidentical Hormones vs Synthetics

Classification of Progestins

Progestins

- **C-21 progestins**
  - Pregnanes
    - Medroxyprogesterone acetate
    - Megestrol acetate
    - Cyproterone acetate
- **19-nor testosterones**
  - Estranes
    - Norethindrone
    - Norethindrone acetate
    - Ethynodiol diacetate
    - Lynestrenol
    - Norethynodrel
  - Gonanes
    - Norgestrel
    - Levonorgestrel
    - Norgestimate
    - Desogestrel
    - Gestodene
- **Spironolactone**
  - Drospirenone

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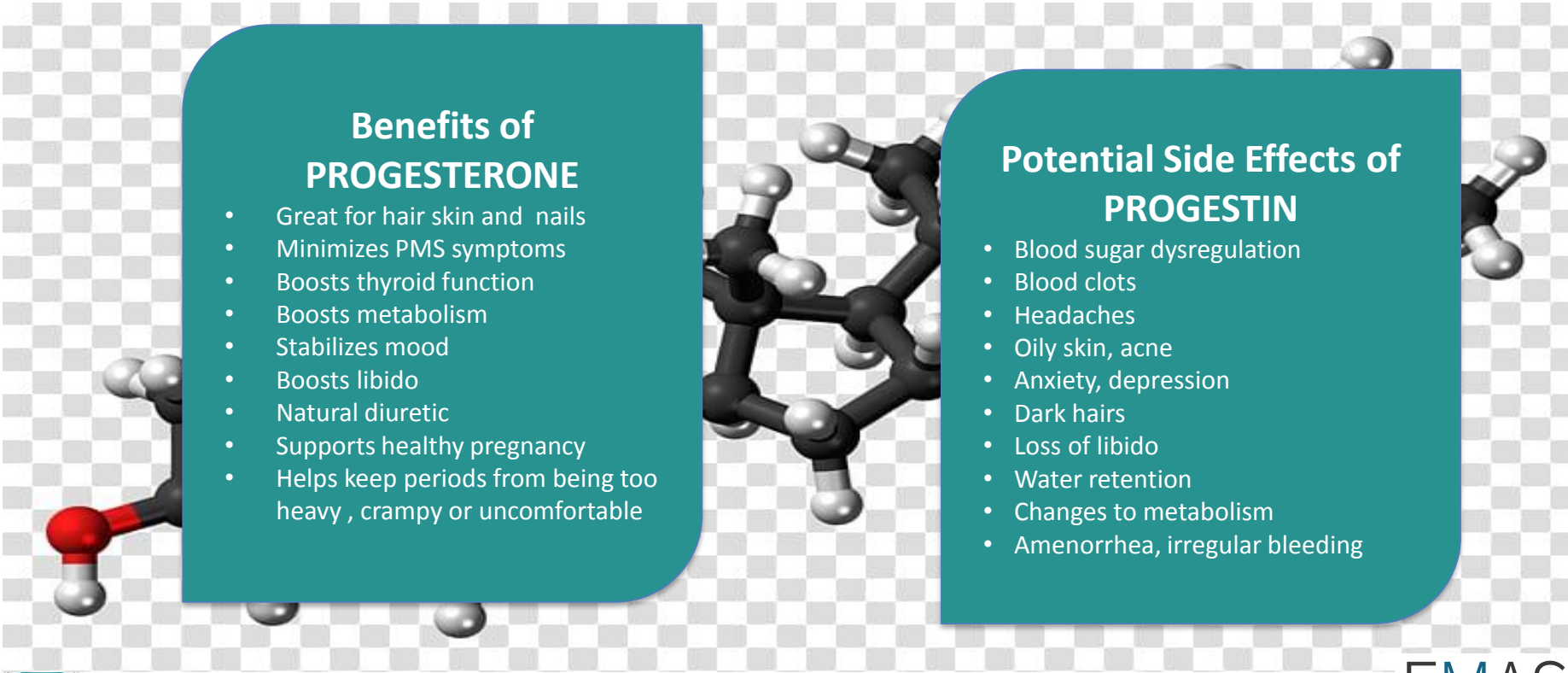
Benefits and Risks



Benefits of PROGESTERONE

- Great for hair skin and nails
- Minimizes PMS symptoms
- Boosts thyroid function
- Boosts metabolism
- Stabilizes mood
- Boosts libido
- Natural diuretic
- Supports healthy pregnancy
- Helps keep periods from being too heavy , crampy or uncomfortable

Potential Side Effects of PROGESTIN

- Blood sugar dysregulation
- Blood clots
- Headaches
- Oily skin, acne
- Anxiety, depression
- Dark hairs
- Loss of libido
- Water retention
- Changes to metabolism
- Amenorrhea, irregular bleeding

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Progesterone vs Progestins

Symptomatic Relief and QOL

- 30% reduction in sleep issues
- 50% reduction in anxiety
- 60% reduction in depression
- 30% reduction in somatic symptoms
- 25% menstrual bleeding
- 40% reduction in cognitive difficulties
- 30% improvement in sexual function

OVERALL 65% felt it worked better

Holtorf, K. (2009). Are bioidentical hormones (estradiol, estriol, and progesterone safer or more efficacious that commonly used synthetic version in hormone replacement therapy? *Postgraduate Medicine, 121*(1). https: //doi.org/10.3810/pgm.2009.01.1949

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Progesterone vs Progestins

Breast Cancer Risk

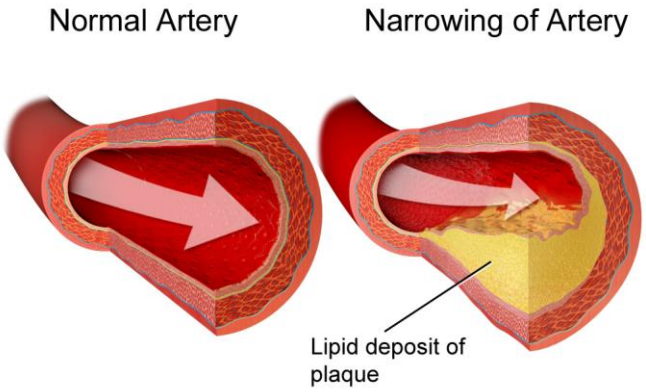
- WHI showed **synthetic progestin** increased risk for breast cancer.
- Nurses Health Study risk of breast cancer 67% when progestin was added
- When estrogen was combined with **progesterone** breast cancer risk dropped to 0.9 relative risk.

Holtorf, K. (2009). Are bioidentical hormones (estradiol, estriol, and progesterone safer or more efficacious that commonly used synthetic version in hormone replacement therapy? *Postgraduate Medicine, 121*(1). https: //doi.org/10.3810/pgm.2009.01.1949

Progesterone vs Progestins

Cardiovascular Risk

- WHI study when Progestin was added to Premarin resulted substantial increase on the risk of stroke and heart attack
- Effects of Progestins
  - Reduction of HDL
  - Vasoconstriction resulting in Coronary spasm
  - Atherosclerotic Plaque formation



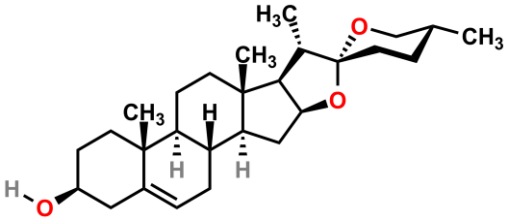
Coronary Artery Disease

Holtorf, K. (2009). Are bioidentical hormones (estradiol, estriol, and progesterone safer or more efficacious that commonly used synthetic version in hormone replacement therapy? *Postgraduate Medicine, 121*(1). https: //doi.org/10.3810/pgm.2009.01.1949

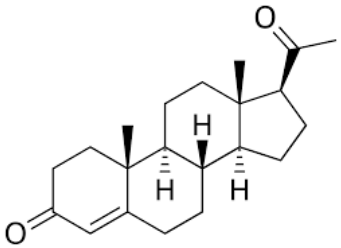
Where do Pellets come from?

Mexican Wild

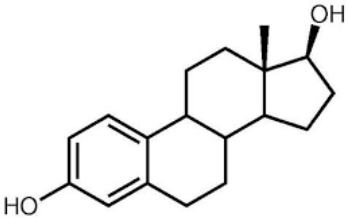
Y



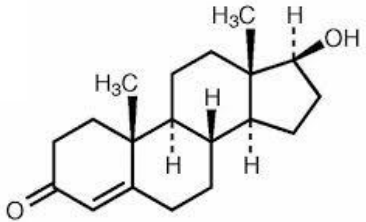
Diosgenin



Progesterone



Estradiol



Testosterone

$C_{19}H_{28}O_2$ MW 288.42

What are Pellets?

- Bioidentical hormones compressed into small cylinders
- Placed in the subcutaneous space through a small skin incision usually in the hip
- Pellets may contain estradiol, progesterone, testosterone, dhea, pregnenolone
- Size varies and is dosing dependent
  (Length 4x12mm Width 3-4 mm)
- Onset of action immediate release
- Clinical response 2 weeks after the insertion

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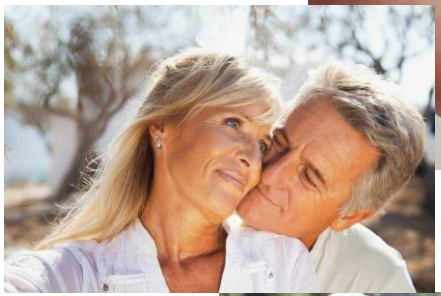
What makes pellets unique?

Subcutaneous delivery (implants)



- By-passes Enteral-Hepatic Circulation
- Does not affect clotting factors
- Increases compliance
- Effective
- Long Lasting 3-4 months

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Formulation and Manufacturing of Pellets

- The original Testosterone Implants were made with high pressure molding of crystalline testosterone mixed with an excipient such as stearic acid to provide lubrication on surface and improve cohesiveness of the hormone crystalized powders to avoid fragmentation. Cholesterol is another option if you are concerned about extrusions related to stearic acid
- Smaller dose hormones such as progesterone and estradiol are made with high pressure molding.
- High Pressure related problems fragmentation encapsulation variable absorption
- Testosterone pellets are made with high temperature molding without need for excipients. Stable release, less fragmentation

Varma, K. (2016). Excipients used in the formulation of tablets. *Research and Reviews: Journal of Chemistry.*

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Physical Features of Implants

Product Name	Length in mm	Width mm
Testosterone 200mg 2% chol	13.97	4.10
Testosterone 100mg 2% chol	12.25	3.25
Testosterone 25mg	3.25	3.00
Testosterone 50mg	6.25	3.00
Progesterone 100mg	12	3.00
Estradiol 15mg	1.75	3.00
Estradiol 20mg	2.0-2.5	3.00

Pellecome
Implanter Trocar Dimensions
Female: 3.5mm ID (4.0 OD) x 43mm
Male: 4.51 mm ID (5.0 OD) x 43mm

WellsRx Pellets

Size Considerations

13.97 X 3= 41.91mm
Less than 43mm

Product Name	Length in mm	Width mm
Testosterone 200mg 2% chol	13.97	4.10
Testosterone 100mg 2% chol	12.25	3.25
Testosterone 25mg	3.25	3.00
Testosterone 50mg	6.25	3.00
Progesterone 100mg	12	3.00
Estradiol 15mg	1.75	3.00
Estradiol 20mg	2.0-2.5	3.00

Pellecome
Implanter Trocar Dimensions
Female: 3.5mm ID (4.0 OD) x 43mm
Male: 4.51 mm ID (5.0 OD) x 43mm

Max capacity for single trocar is 43mm
Max Male is 3 Testosterone 200
Testosterone 200 won't fit into Female trocar

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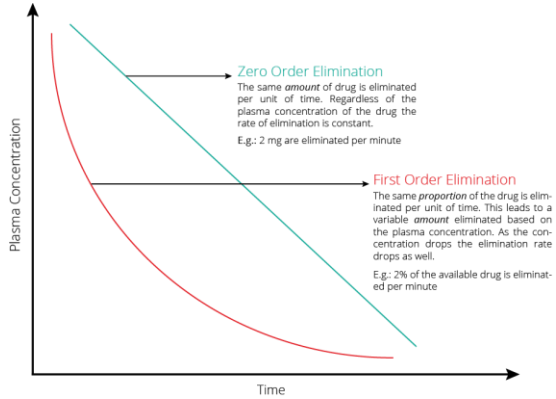
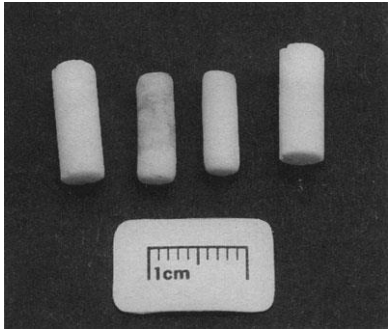
Mechanism of Absorption

- Uniform erosion of the pellet surface preserving cylindrical shape
- The larger surface area the greater the absorption
- Surface area is the rate limiting factor for Testosterone absorption
- Factors that unpredictably increase surface area and absorption
  - Fragmentation
  - Crushing
  - Pitting (soft pellets)
- Other factors affecting absorption
  - Tissue trauma
  - Foreign body tissue reaction encasing the pellet





The two un-implanted 200 mg pellets (left and right sides) are shown in comparison with two 200 mg pellets which were extruded 43 (left) and 62 (right) days after implantation

Testosterone-action, deficiency, substitution E. Nieschlag, H. M. Behre (eds.) Springer-Verlag Berlin Heidelberg 1990
Pharmacology of testosterone pellet implants David J. Handelsman

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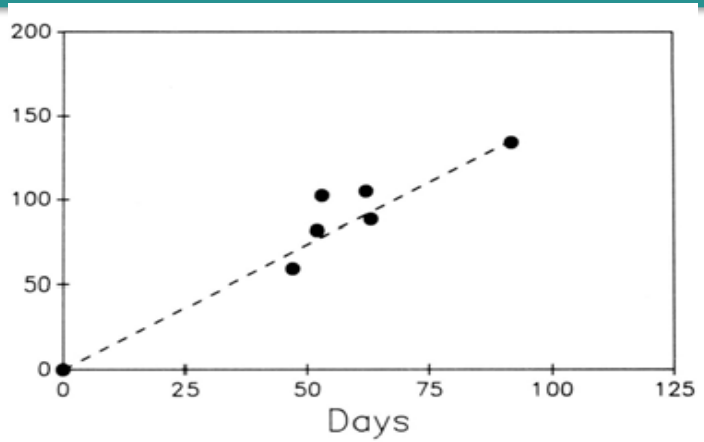
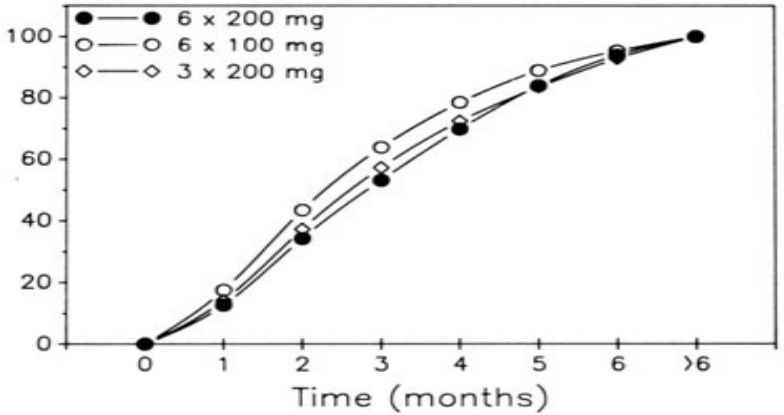
Kinetics of Absorption





- Extruded pellets were cleaned, dried, weighed, and plotted to determine release rate per day based on mass of testosterone release compared to un-implanted 200mg pellets.
- These curves provided an estimate of 2.5 months for the effective half-time of absorption and calculated release rate of 0.65 mg /day/100 mg pellet.
- Neither the size nor the number of pellets influenced the rate of testosterone absorption

Testosterone-action, deficiency, substitution E. Nieschlag, H. M. Behre (eds.) Springer-Verlag Berlin Heidelberg 1990
Pharmacology of testosterone pellet implants David J. Handelsman

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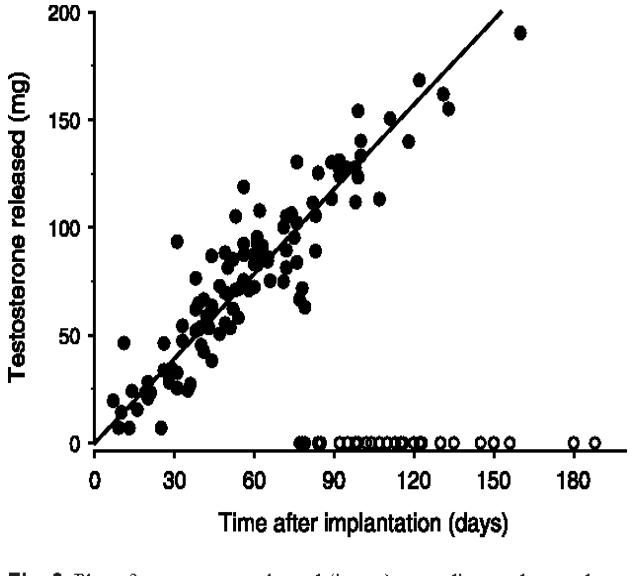
In Vivo Testosterone release rate and duration of action of Testosterone Implants

Summary of study

- 3 Randomized controlled trials
- Collection of extruded Pellets
- 136 Androgen-deficient men
- Standard dose 800 mg of pure Testosterone pellets , no excipients
- Re-insertions every 5-7 months
- Testosterone release rate was estimated by measuring the dry weight lost by pellets (n-179) over their time in situ.
- The loss of dry weight of intact (n-112) pellets strongly correlated with time in situ providing an estimated daily testosterone release rate of 1.34 mg per day per 200 mg pellet for the the first 3 months
- The duration of action is about 6 months in uncomplicated cases



Testosterone release rate and duration of action of Testosterone Implants
Endocrinol (Oxf) 2004 Ap;60(4);420-8

Bioavailability of Testosterone Implants

Definition - Availability of the the drug to the general circulation, determined by Plasma Concentration

- By 6 months virtually all the testosterone from the 600 mg pellet and about 90% of that in the 1200 mg pellets was absorbed
- Consistent with near complete bioavailability, net testosterone release is closely correlated with pellet dose (r=0.999)
- 6 x 200 mg dose regimen gives twice that of either 6x 1 00 mg or 3 x 200 mg regimen, the latter two of which gave very similar net release of testosterone.

Testosterone-action, deficiency, substitution E. Nieschlag, H. M. Behre (eds.) Springer-Verlag Berlin Heidelberg 1990. Pharmacology of testosterone pellet implants David J. Handelsman

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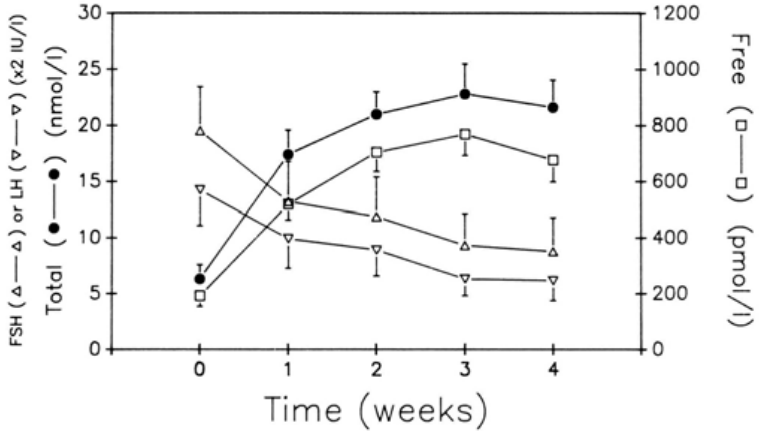
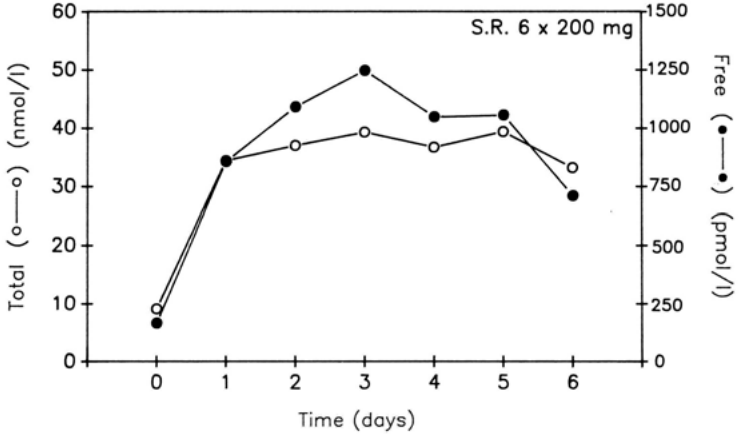
Weekly & Daily Testosterone Levels after Testosterone Pellet Insertion



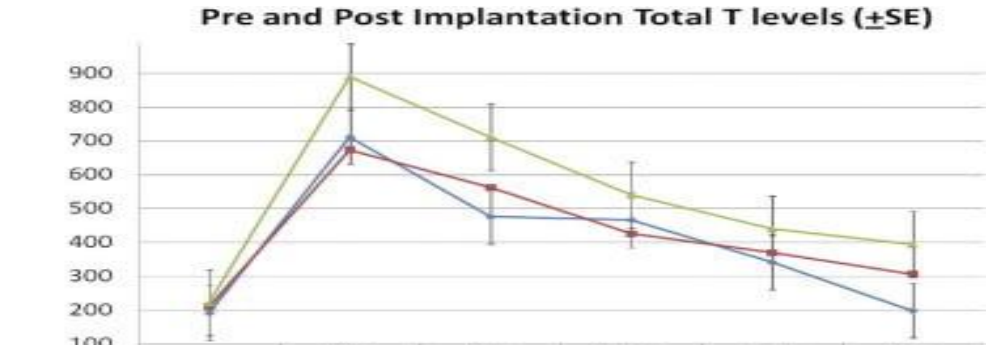
Total (closed circles) and free (open squares) testosterone and LH (open triangle) and FSH (open inverse triangle/e) in 15 hypogonadal men having blood sampled at weekly intervals for the first months after undergoing implantation of 6 x 100 mg testosterone pellets. Gonadotropins are plotted only for the 9 men with primary (hypergonadotropic) hypogonadism. Note the smooth rise of testosterone and suppression of gonadotropins without evidence of initial burst release of testosterone.



Total (closed circles) and free (open circles) testosterone in one hypogonadal man undergoing daily blood sampling for a week after implantation of 6 x 200 mg pellets. Note the lack of initial burst release of testosterone with plateau levels achieved after the first day and maintained steadily throughout the week

Testosterone-action, deficiency, substitution E. Nieschlag, H. M. Behre (eds.) Springer-Verlag Berlin Heidelberg 1990
Pharmacology of testosterone pellet implants David J. Handelsman

Monthly Testosterone Levels after Testosterone Pellet Insertion



	Pre	One Month	Two Months	Three Months	Four Months	Five Months
6 and 7	192	712	476	467	342	199
8 and 9	210	674	563	426	370	307
10 to 12	222	890	711	540	441	394

Differences between levels were significant during the first and second months after implantation for the 10 and 12 pellet group ($p<0.02$) and the other two groups. Differences between the 8 and 9 and 6 and 7 groups were not significant at any time period. Low numbers precluded statistical comparison for the time periods longer than five months.

Journal of Urology Sexual Function/Dysfunction/Andrology: Medical and Non-Surgical Therapy II1 Apr 2010

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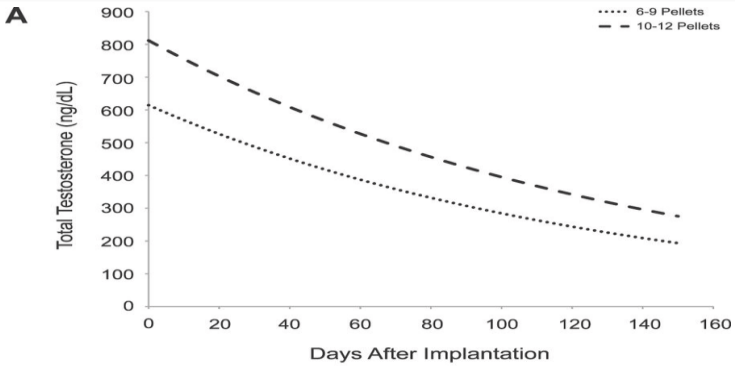
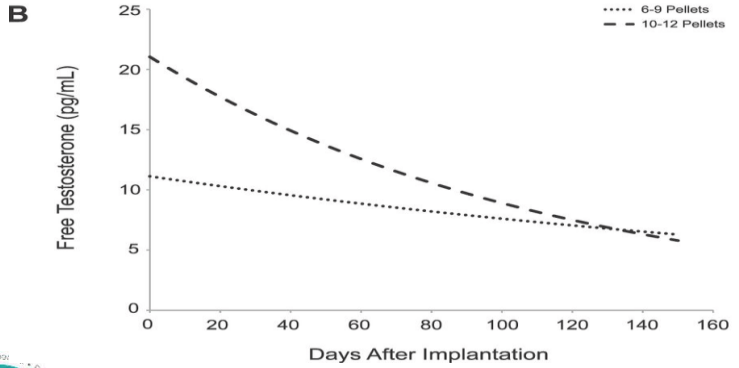
Free and Total Testosterone Levels after Testosterone Pellet Insertion

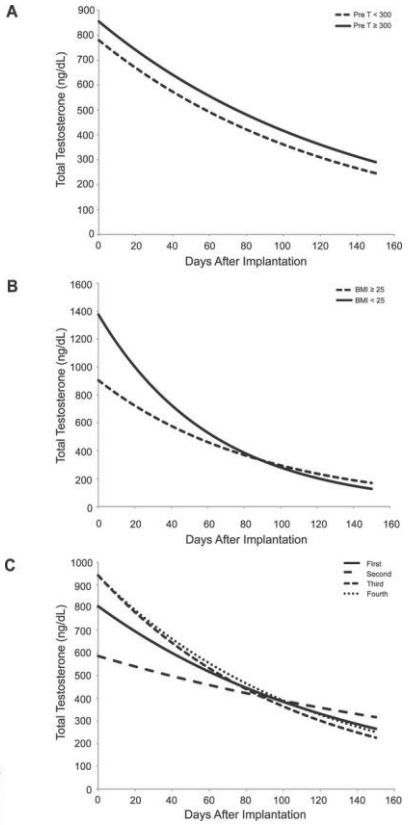


Total testosterone decay curves. **(A)** Plot of extrapolated total testosterone vs days after implantation for all patients and patients receiving 6 to 9 and 10 to 12 pellets using the curve fit equations



(B) Plot of extrapolated free testosterone vs days after implantation for all patients and patients receiving 6 to 9 and 10 to 12 pellets.

Testosterone Levels - BMI – Sequential Implantations



Testosterone (T) decay as a function of preimplantation T, body mass index (BMI), and sequential implantations.

(A) Plot of extrapolated total T vs days after implantation for patients receiving 10 to 12 pellets, separated by men with preimplantation T <300 and ≥300 ng/dL.

(B) Plot of extrapolated total T vs days after implantation for patients receiving 10 to 12 pellets, separated by BMI group.

(C) Plot of extrapolated total T vs days after implantation for patients receiving 10 to 12 pellets based on sequential implantations.

Alexander W. Pastuszak . Pharmacokinetic Evaluation and Dosing of Subcutaneous Testosterone Pellets

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