COMPOUNDED TESTOSTERONE THERAPY IN WOMEN

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Outline

- Critical role of testosterone (T)
- Necessity
- Safety and efficacy T implant therapy
- Data on testosterone implants (PK)

Hormone levels (controversies)

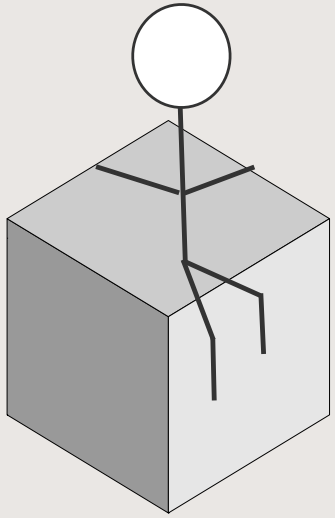
The industry

Issues and controversies

  Estradiol pellets, PK studies

“Difference of opinion leads to enquiry,
and enquiry to truth;
and that, I am sure, is the ultimate and
sincere object of us both.”

Thomas Jefferson 1815



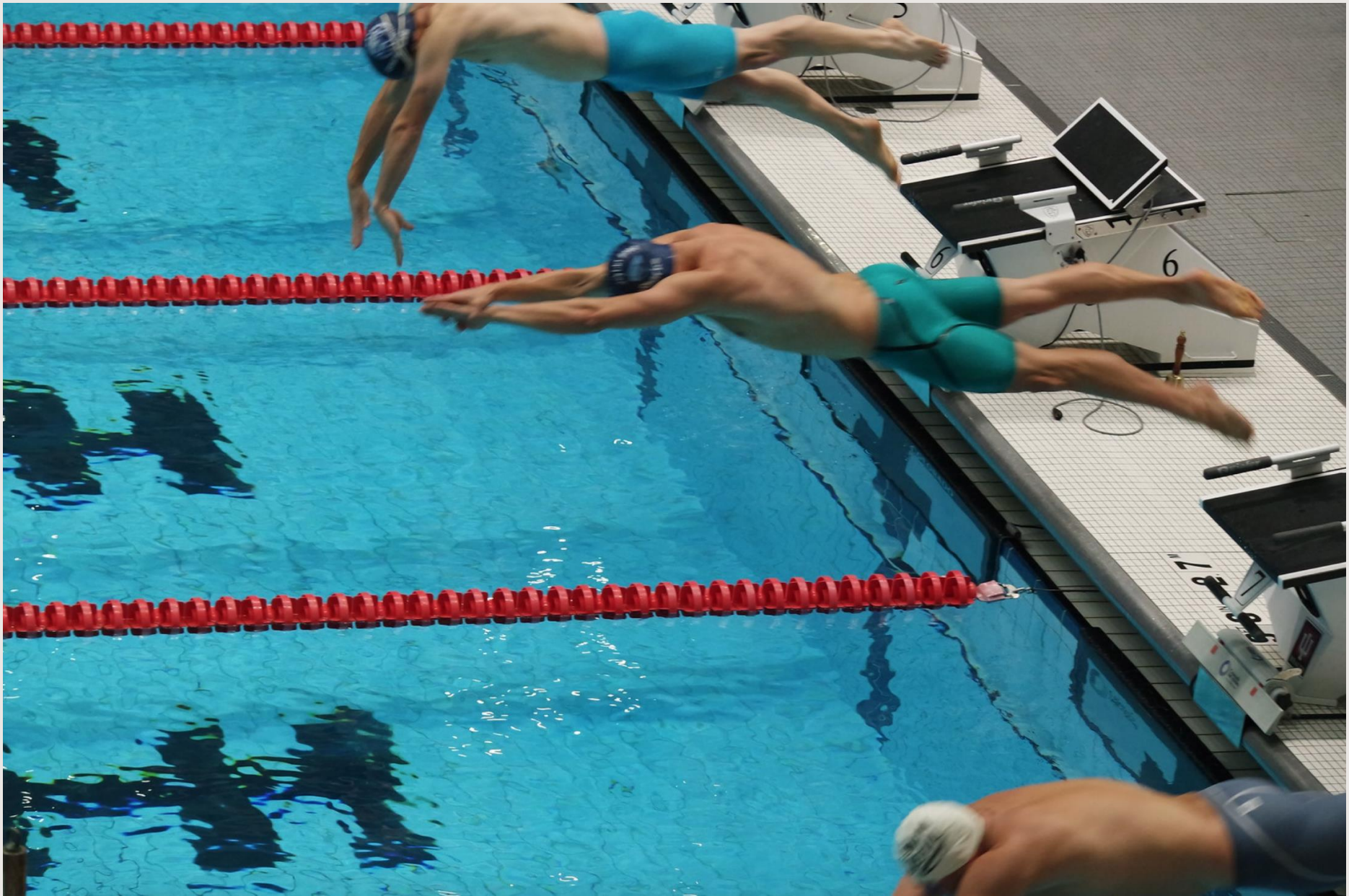
BACKGROUND

Critical role of testosterone

Sex drive and libido

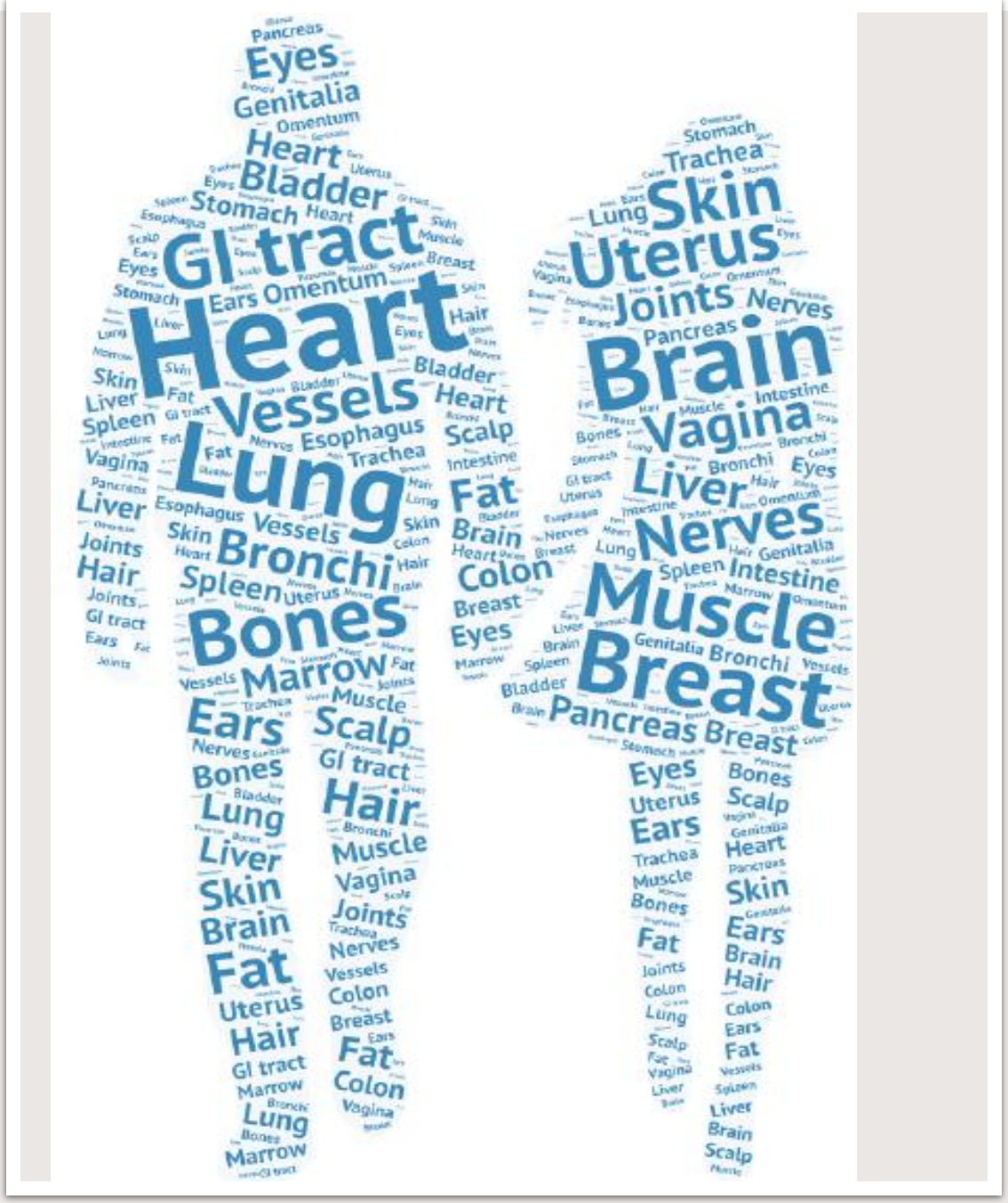
‘Low T’

Lean muscle mass, strength, co-ordination, confidence (both sexes)

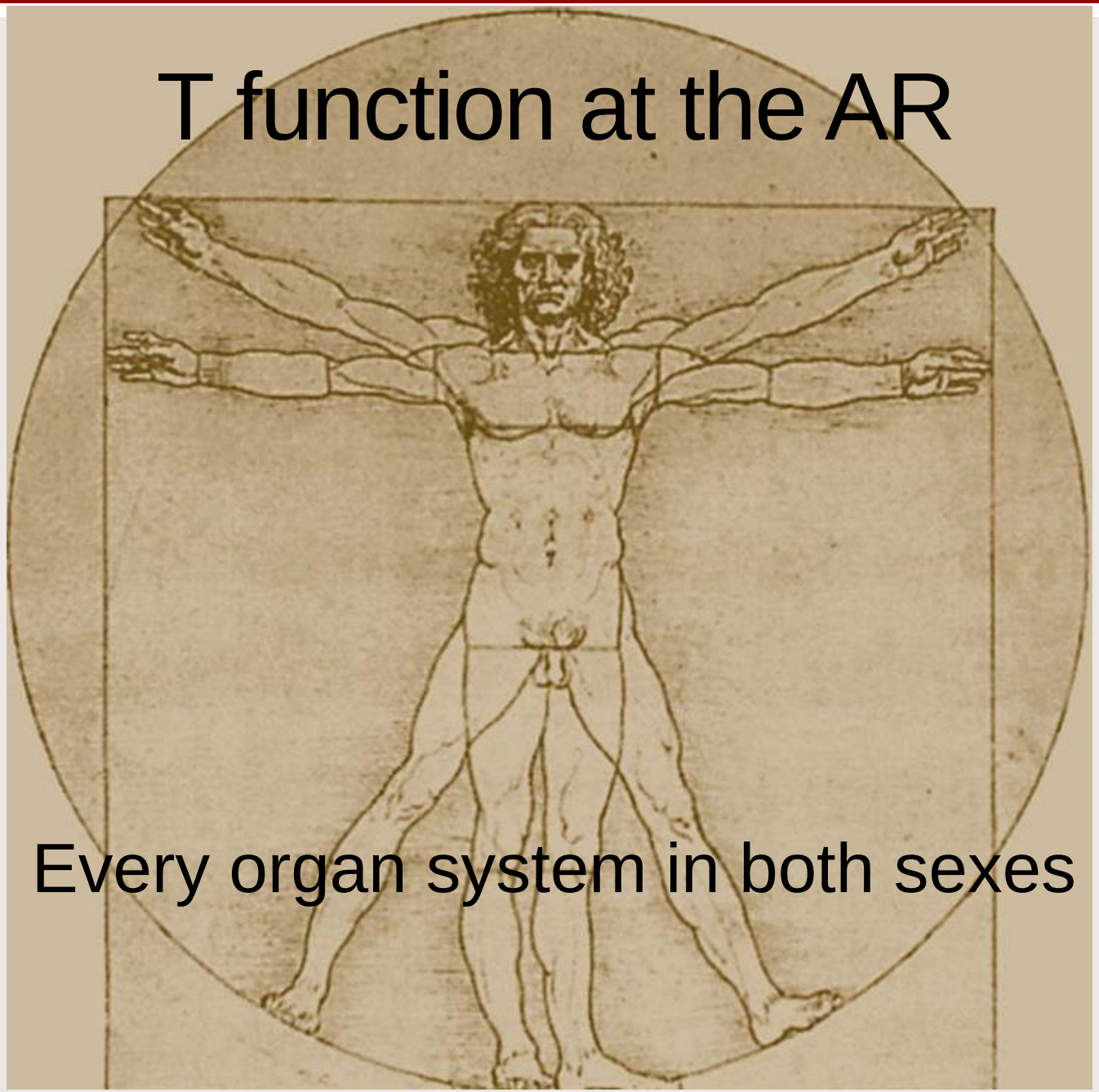


Androgen Receptors

Every organ system in both sexes



T function at the AR



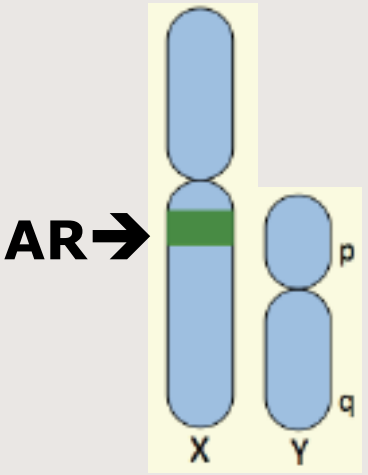
Every organ system in both sexes

Testosterone (T)

- Most abundant active hormone in both sexes

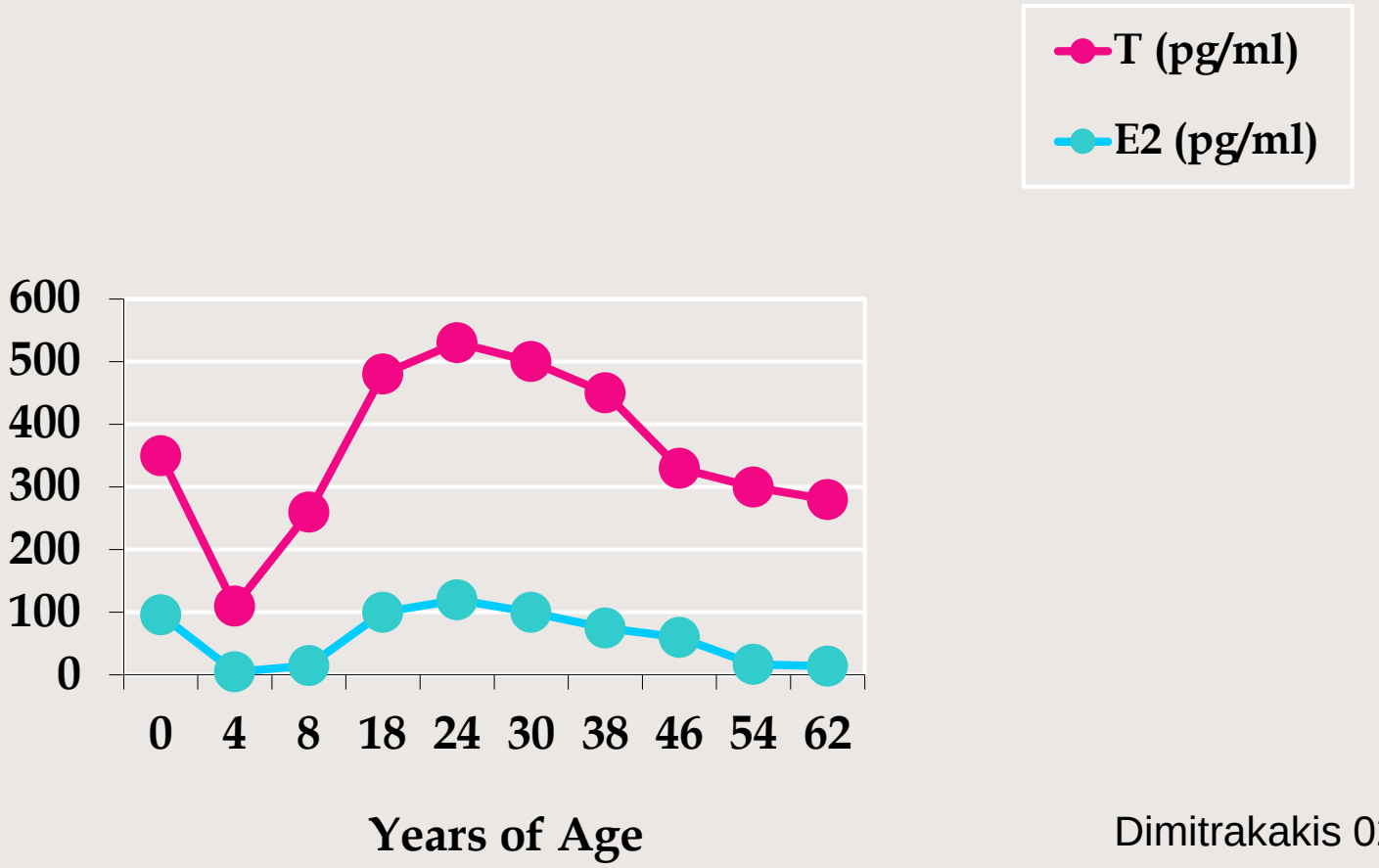
  Direct effect at the androgen receptor (AR)

  Peripheral conversion of T is major source of estrogen in men and postmenopausal women



Testosterone > Estradiol levels

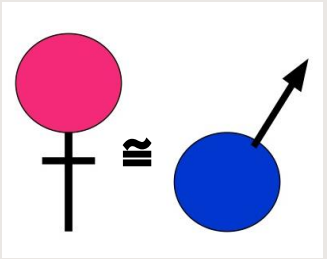
Throughout the entire female lifespan



Dimitrakakis 02

Adrenal androgens, pro-hormones

Major source of T at the cellular level **(75% of T)**



Androstenedione

Reference Range

Adult Male

18-30 Years 50-220 ng/dL

31-50 Years 40-190 ng/dL

Adult Female

Follicular 35-250 ng/dL

Luteal 30-235 ng/dL

DHEA

Reference Range

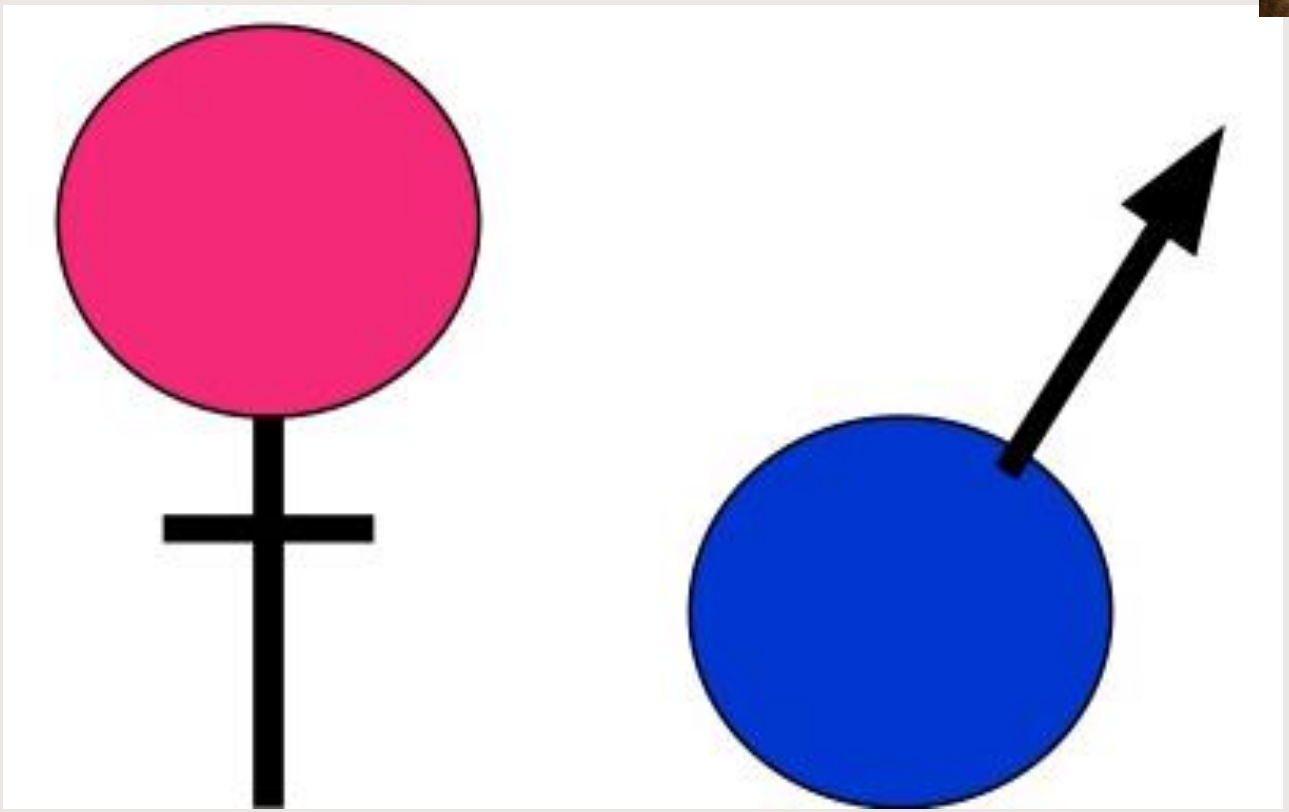
Adult Male

61-1636 ng/dL

Adult Female

102-1185 ng/dL

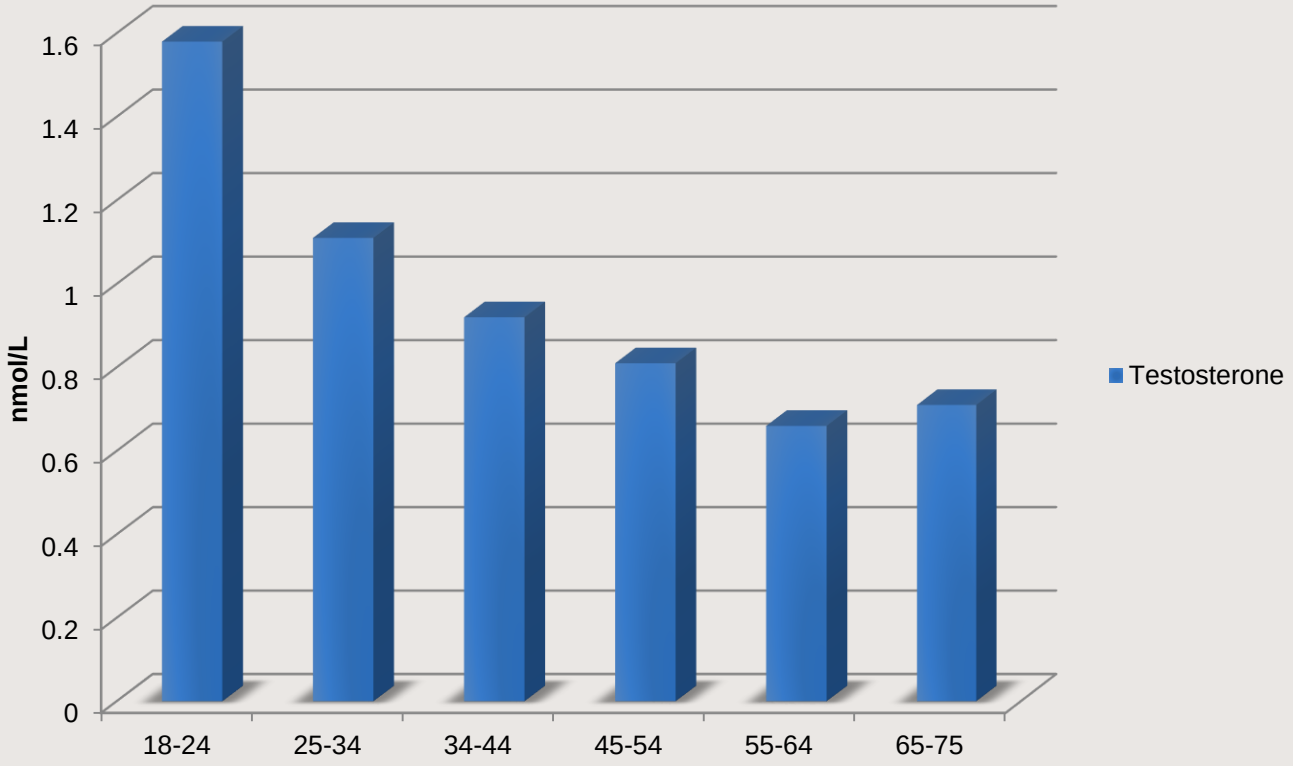
Androgens decline with age



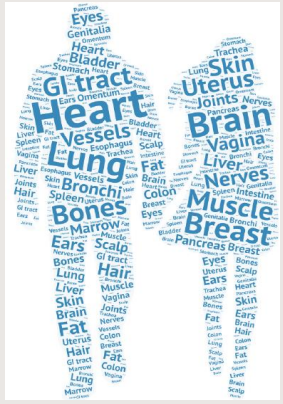
Testosterone

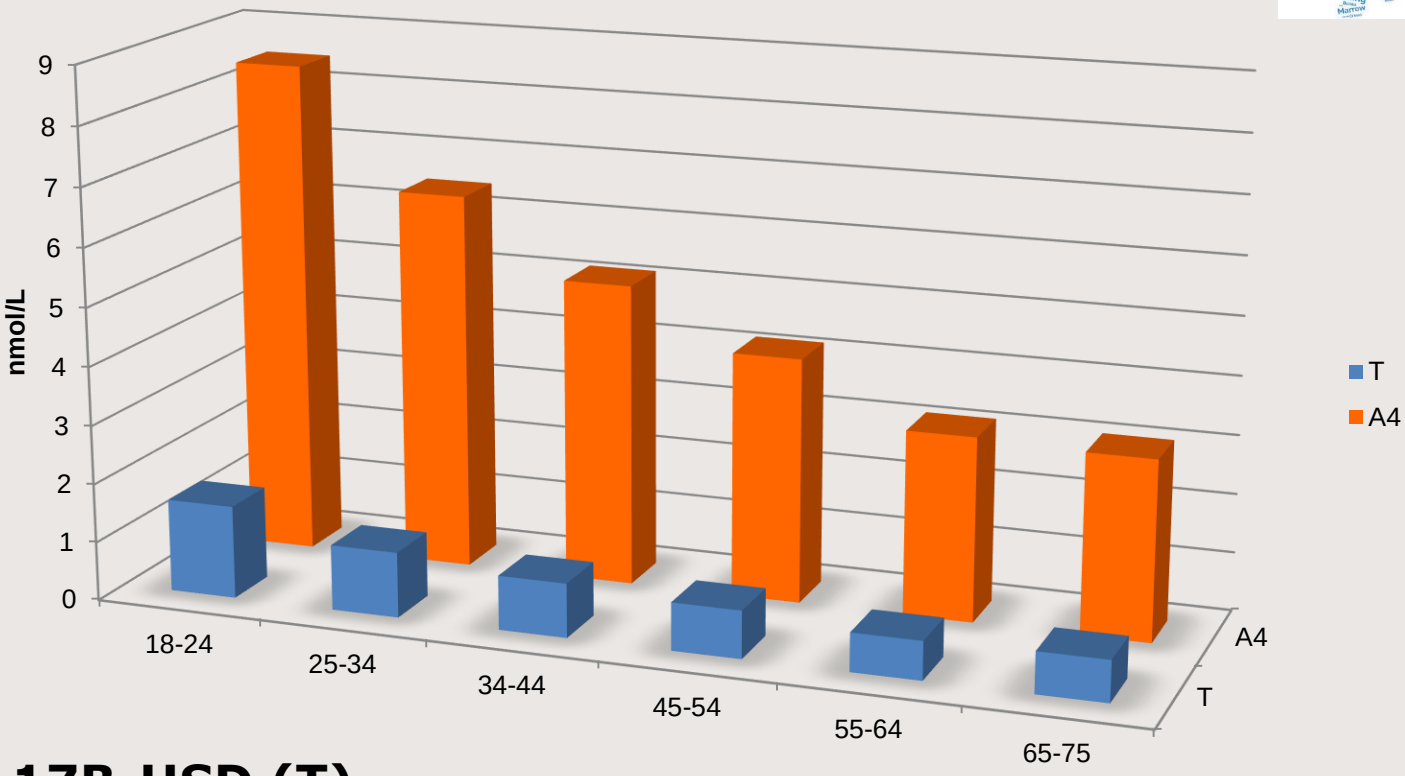
Peaks in women in their twenties

Gradual decline



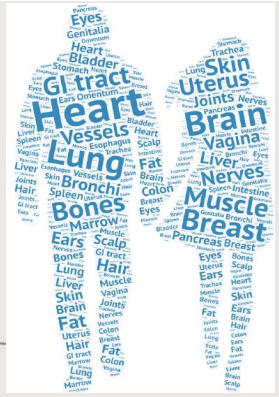
Androstenedione (A4)

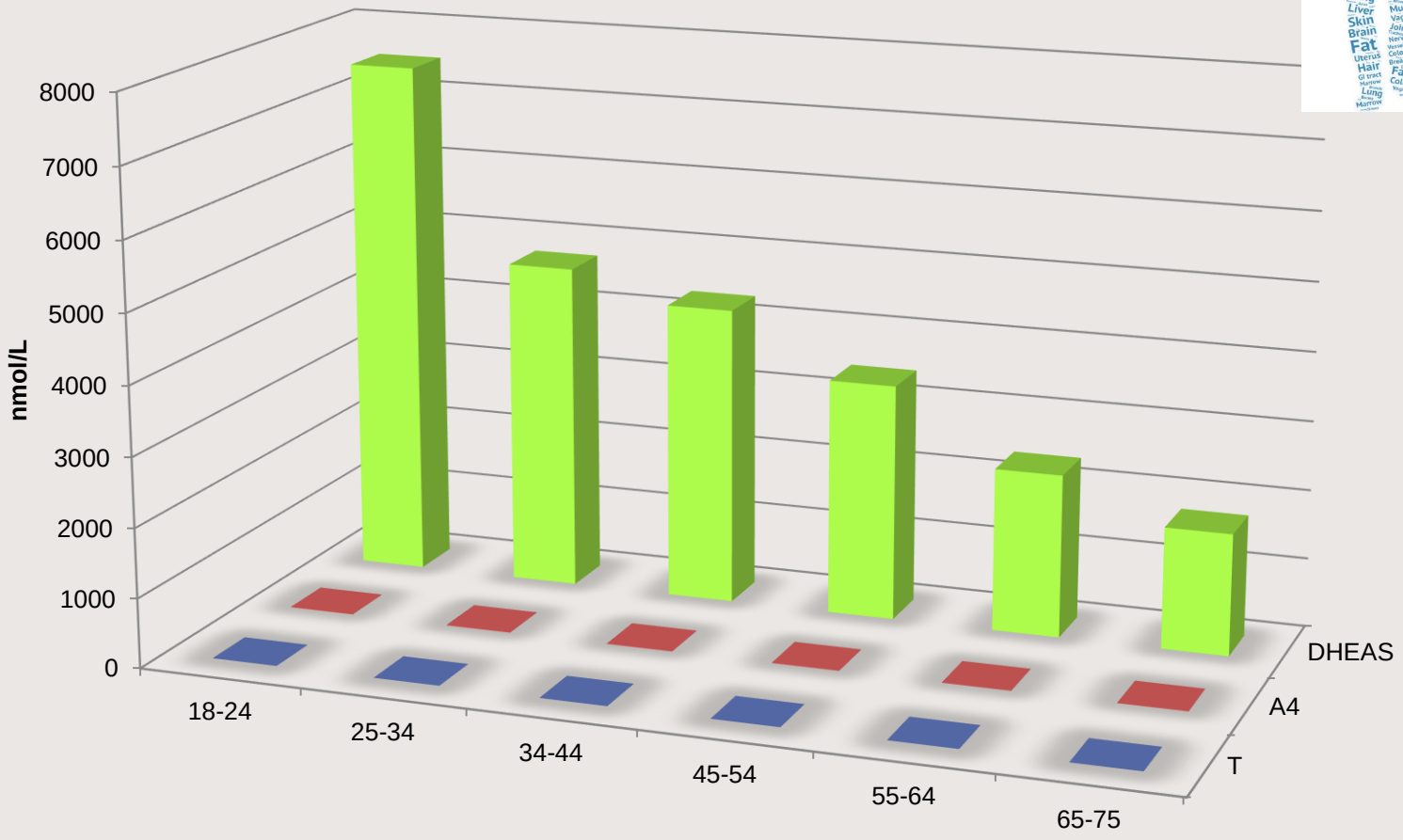




17B-HSD (T)
Aromatase (E1)

DHEA(S)





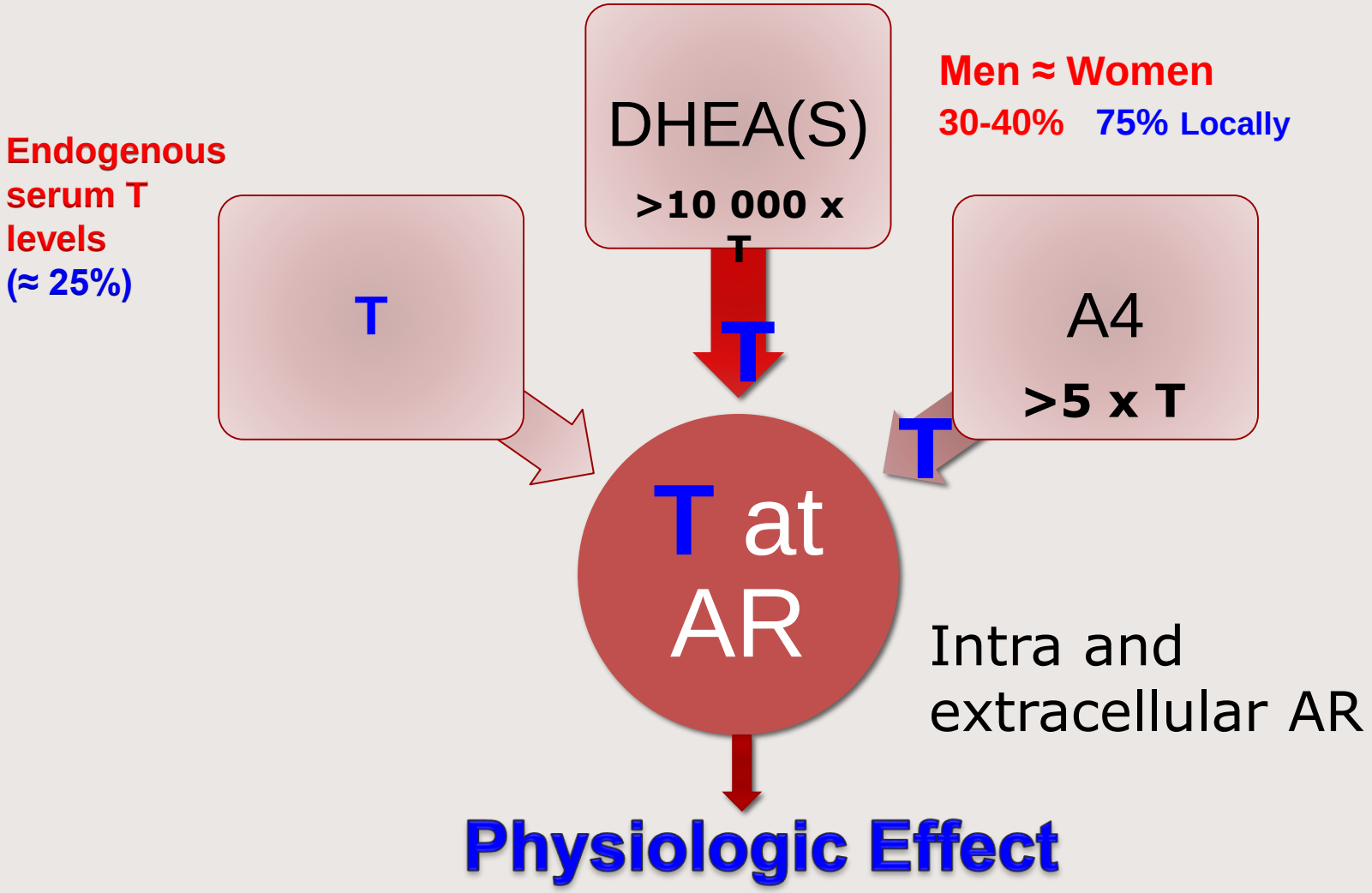
3B-HSD (A4)➔17B-HSD (T)
17B-HSD (Adiol)➔3B-HSD (T)

Labrie 17

- Serum testosterone is not a valid marker of androgenic activity in women
- ...it is not surprising that despite long series of prospective and case-control cohort studies performed during the last 30 years, a correlation between serum testosterone and any clinical condition believed to be under androgenic control in women has remained elusive.

Controversial guidelines

TRT: Serum T + DHEA(S) + Androstenedione



Symptoms of androgen deficiency

Men and Women (pre and post menopausal)

- Physical fatigue, exhaustion
- Bone loss
- Muscle wasting
- Fat accumulation
- Thin, dry skin, wrinkles, brittle hair and nails
- Chronic pain, muscle aches, stiffness

Symptoms of androgen deficiency

- Urinary incontinence, frequency, urgency
- BPH
- Vaginal atrophy
- Decreased sex drive and libido
- Impotence (decreased performance)

Symptoms of androgen deficiency

- Dysphoric mood
  - Depression, anxiety, irritability, loss of confidence
- Sleep disturbance, insomnia
- Vasomotor instability (hot flashes)
- Cognitive changes, decreased mental focus
- Memory loss
- Increased inflammation

Age associated diseases, T beneficial effect

- Obesity
- Coronary artery disease, CHF
- Pulmonary disease, asthma, COPD
- Insulin resistance, diabetes, metabolic syndrome
- Cancer (immune function)
- Neurological diseases, dementia
- Osteoporosis, sarcopenia

NECESSITY

There is no FDA approved USP testosterone product for women in the United States

Compounded vaginal cream

Testosterone with estriol (E3)

Testosterone, estriol, and progesterone

Testosterone (± P)

- Initially began using in breast cancer patients for urogenital symptoms over 20 years ago
- Non BCA patients
- Vaginal dryness, urinary urgency, frequency, painful sex, etc.
- Systemic symptoms

DATA

Glaser RL, Zava DT, Wurtzbacher D. Pilot study: absorption and efficacy of multiple hormones delivered in a single cream applied to the mucous membranes of the labia and vagina. Gynecologic and obstetric investigation. 2008;66:111-118.

USP Estriol (E3)

- Low binding affinity for myometrium and breast
- High binding affinity in bladder and vagina
- Vaginal estriol does not increase the risk or recurrence of breast cancer
- Does not accumulate
- OTC in Europe
- Only available in compounded preparations in the US

Lack of data on the efficacy of topical estriol (skin)

Affordable care

Product	Cost of Rx	Number Doses	Cost per dose	Dosing	Cost per month
Vagifem®	$176.86 with coupon	8	**$22.10**	1 daily for 2 weeks then twice weekly	$176.86 ($397.80 1st month)
Generic vaginal estradiol	$146.33 $63.07 with coupon	8 8	**$18.29** **$7.88**		$63.06-$146.33 ($329.22 1st month)
Intrarosa® Vaginal DHEA 6.5 mg	$248.32 $208.38 with coupon	28 28	**$8.87** **$7.44**	Once daily	$208.38-$248.32
Compounded Vaginal DHEA tablet 10 mg	$35.00* $52.73*	30 90	**$1.16** **$0.59**	Once daily	$32.48 28d $16.52
Compounded Vaginal DHEA cream 20 mg/gm	$40.01 30 grams	60	**$0.67**	0.5 g daily	$18.76 28d
Compounded T + Estriol Cream	$40.95* 30 grams	120	**$0.34**	0.25 g daily for 14 d then 2-3 times weekly	$4.08 if 3x weekly $10.20 if daily

Compounded T pellets, 80 years

1937 US both sexes

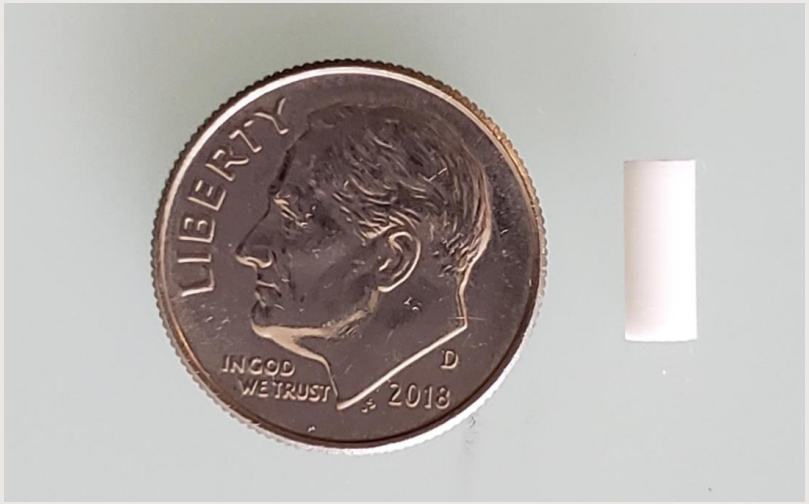
-Therapy for BCA

- Compressed T powder
- 1972 FDA approved 75 mg T pellet, Testopel®
- 50, 100, and 200 mg T pellets Europe and Australia
- Implants used in women (US) are compounded

Compounded formulations

T +Anastrozole (AI)

T + Finasteride



Greenblatt 1949 AJOG

…implantation of hard compressed pellets of crystalline steroids resulted in a slow and more physiologic absorption of the hormone

"…endogenous mechanism of hormonal secretion is more nearly approached and the physiologic action of the hormone more closely imitated."

Indications for T pellets - 70 years

- Menopausal symptoms in whom estrogen therapy has proved unsatisfactory or is contraindicated
- Prevent uterine bleeding
- Endometriosis
- Fibroids
- Nocturia
- Low libido
- Carcinoma of the breast
- Addison’s disease

- Anorexia

Breast cancer patients

- It would be impossible to adequately treat breast cancer survivors without compounded formulations

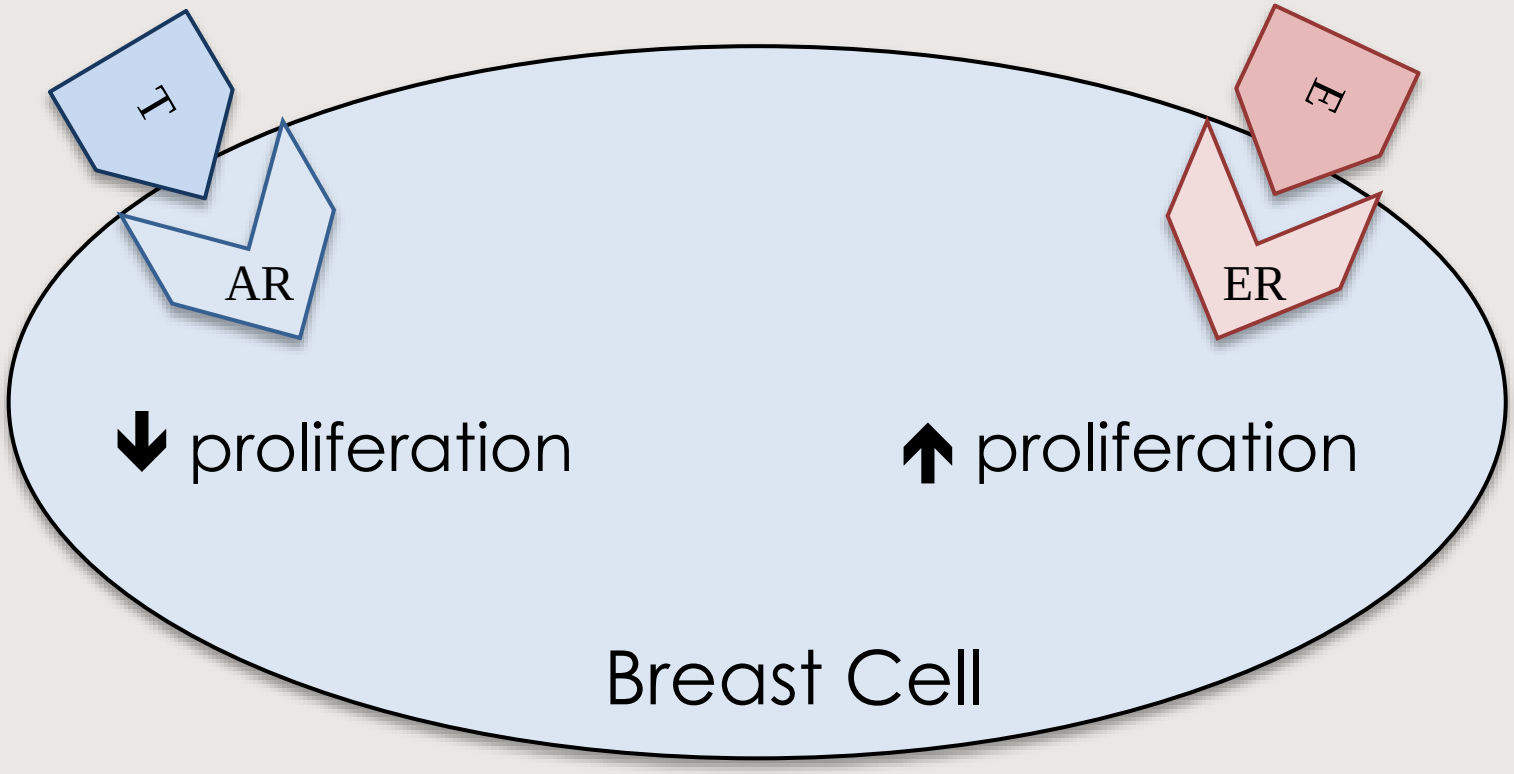
  Compounded vaginal testosterone ± estriol cream ± progesterone

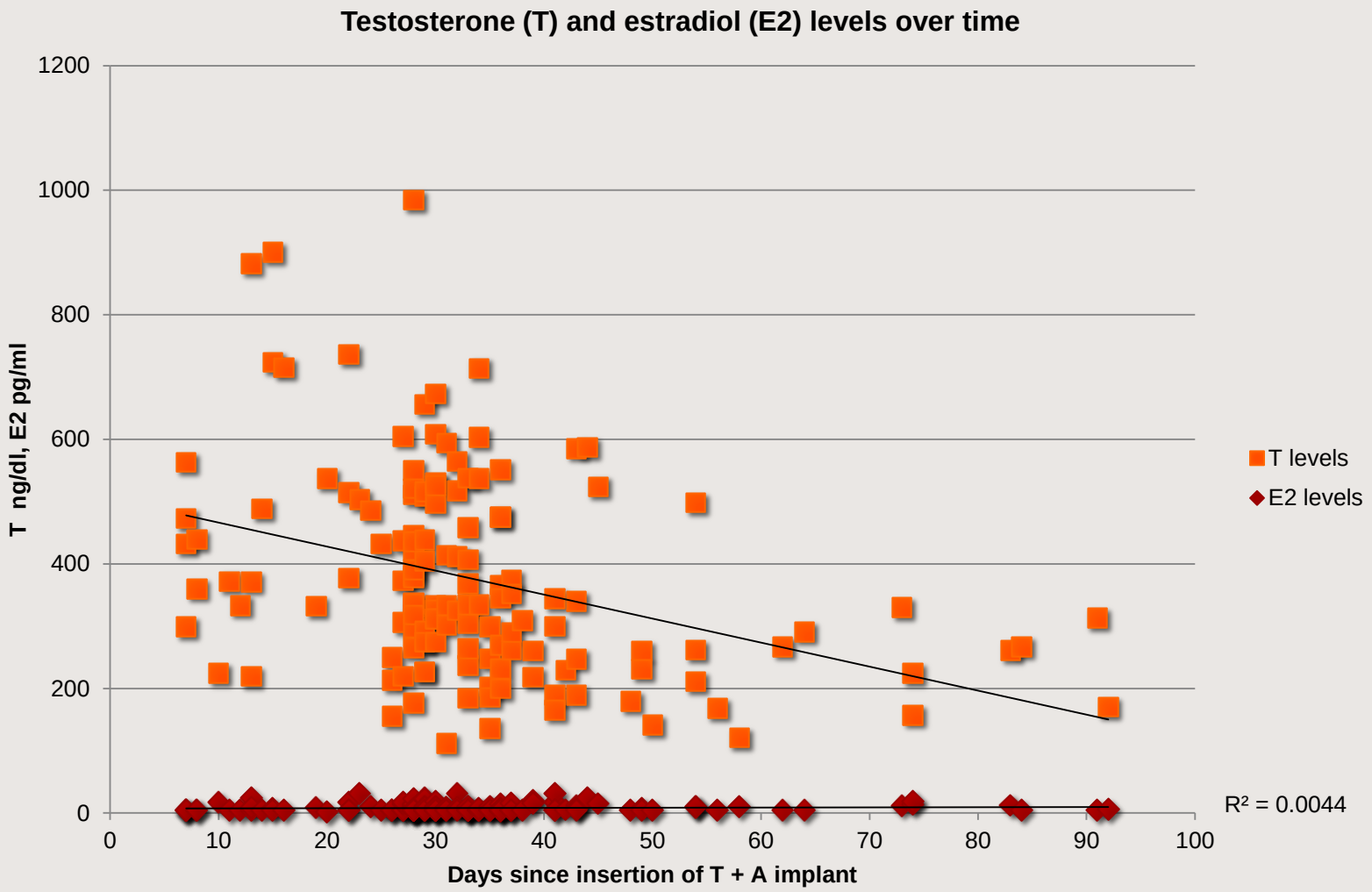
- T + anastrozole (an aromatase inhibitor) combination implant (2009)
- DATA presented at ASCO 2010

‘The combination of testosterone with anastrozole, delivered subcutaneously, provides therapeutic levels of testosterone without elevating estradiol levels’.

Testosterone → Estradiol

Aromatase




Testosterone (T) and estradiol (E2) levels over time
T ng/dl, E2 pg/ml
1200
1000
800
600
400
200
0
0
10
20
30
40
50
60
70
80
90
100
Days since insertion of T + A implant
T levels
E2 levels
R² = 0.0044

ASCO Breast cancer symposium 2014

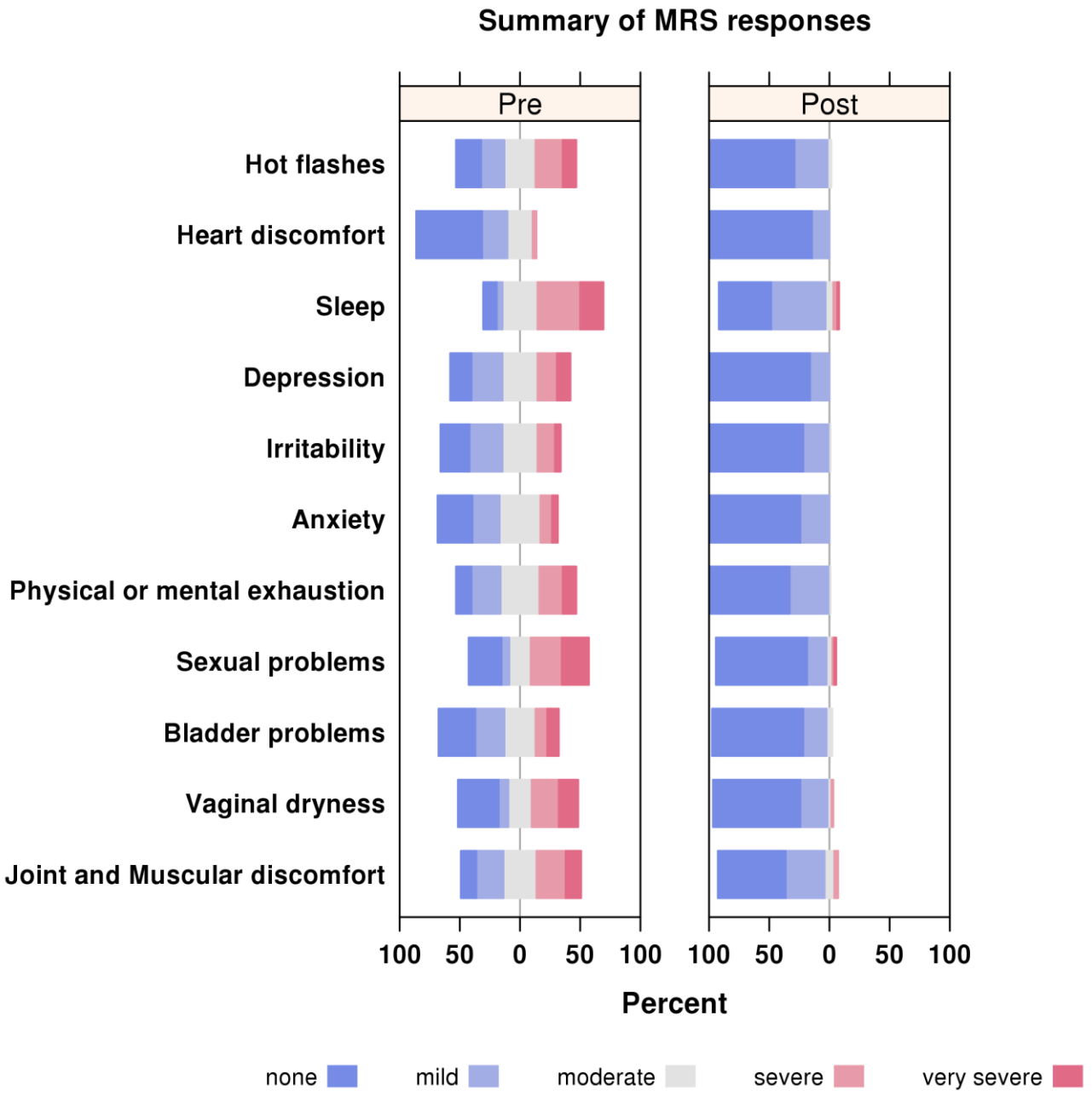
- Efficacy of subcutaneous T on symptoms in BCA patients
  - Validated QoL questionnaire (MRS)
- Prospective study
  - BCA patients (Stage 0-4)
  - Compounded Testosterone + Anastrozole (A) implants
  - Documented therapeutic T levels on therapy

Glaser R, Dimitrakakis C. Efficacy of subcutaneous testosterone on menopausal symptoms in breast cancer survivors. J Clin Oncol 32, 2014 (suppl 26; abstract 109)

ASCO 2014

- No ADE
- No disease recurrence

Age at diagnosis (y)	50.04 ± 10.66 (31.25-90.26)
Age at first insertion (y)	57.17 ± 10.51 (31.74-90.28)
Treatment years	3.93 ± 2.41 (0.11-8.37)
BMI	26.03 ± 4.69
Testosterone dose (mg)	168.89 ± 32.25
Anastrozole dose (mg) (n)	4 (5), 8 (66), 12 (1)
Testosterone level (ng/dl)	354.42 ± 149.06
Stage-0, 1, 2, 3, 4 (n)	15, 25, 23, 6, 3
Disease recurrence (n)	0
Disease progression (n)	1


Summary of MRS responses
Pre
Post
Hot flashes
Heart discomfort
Sleep
Depression
Irritability
Anxiety
Physical or mental exhaustion
Sexual problems
Bladder problems
Vaginal dryness
Joint and Muscular discomfort
100
50
0
50
100
100
50
0
50
100
Percent
none
mild
moderate
severe
very severe

Quality of Life

60 yo metastatic BCA 5/2015

Symptoms:	none	mild	moderate	severe	extremely severe
Score =	0	1	2	3	4
	—		controlled c Cele		
1. Hot flashes, sweating (episodes of sweating)	☒	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☒	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early)	☐	☐	☐	☐	☒
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☒
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☒
6. Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☒
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☒
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☒
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☒	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☒
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☒

On T + L implant therapy 11/2017

(Off Vicodin, Ativan, Ambien)

Symptoms:	none	mild	moderate	severe	extremely severe
Score =	0	1	2	3	4
1. Hot flashes, sweating (episodes of sweating)	☒	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☒	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early)	☒	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☒	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☒	☐	☐	☐	☐
6. Anxiety (inner restlessness, feeling panicky)	☒	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☒	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☒	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☒	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☒	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☒	☐	☐	☐

Quality of life

3.5 years T + L

Thriving

Compounded implants:

T 240 mg +
Letrozole 12 mg

Finasteride 6 mg

Survival

- This patient wouldn’t be alive….

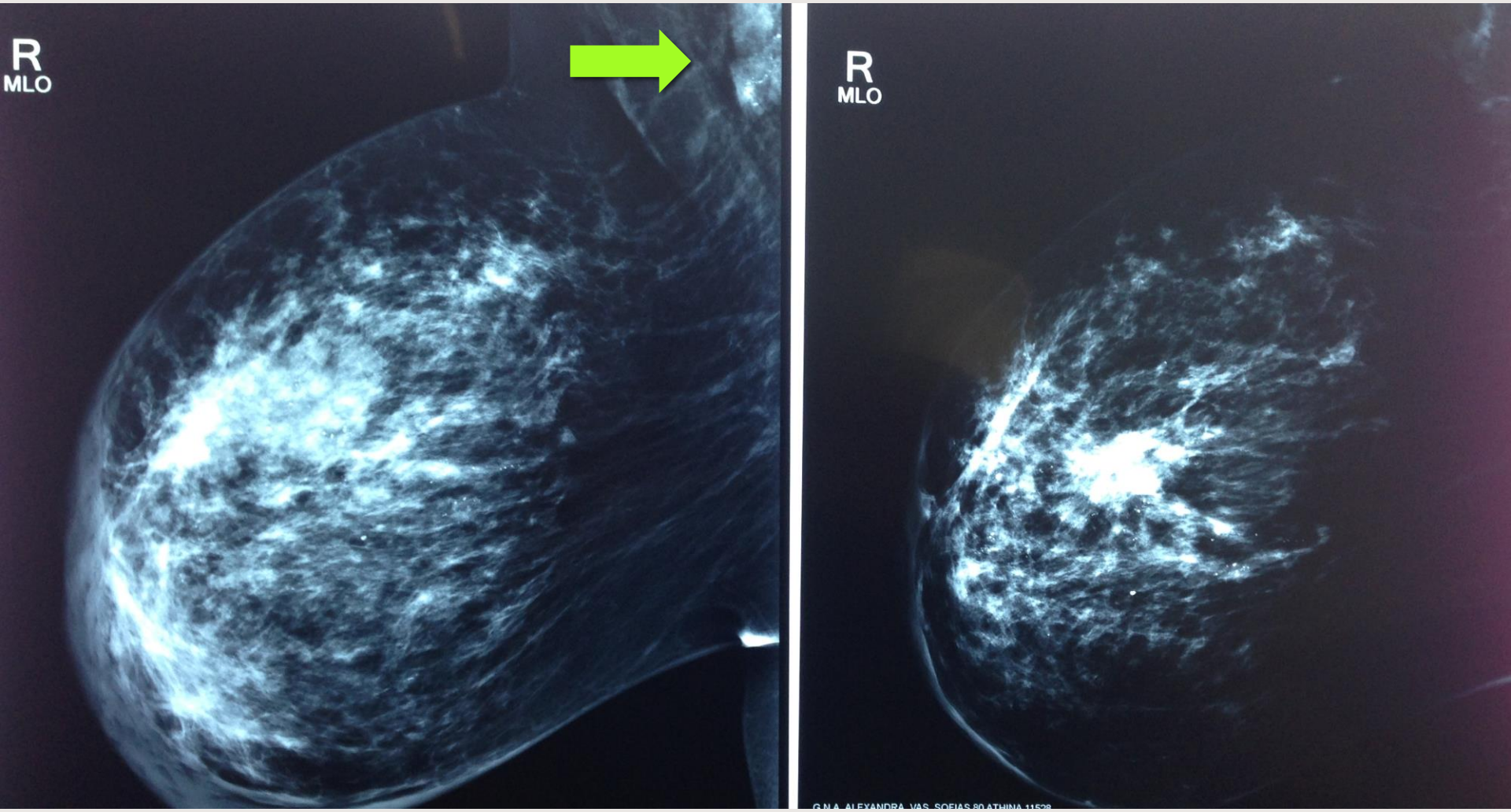
Therapy for breast cancer

Glaser RL, Dimitrakakis C. Rapid response of breast cancer to neoadjuvant intramammary testosterone-anastrozole therapy: neoadjuvant hormone therapy in breast cancer. Menopause (New York, NY). 2014;21:673.

82 y.o. patient (180 mg T + 12 mg A)

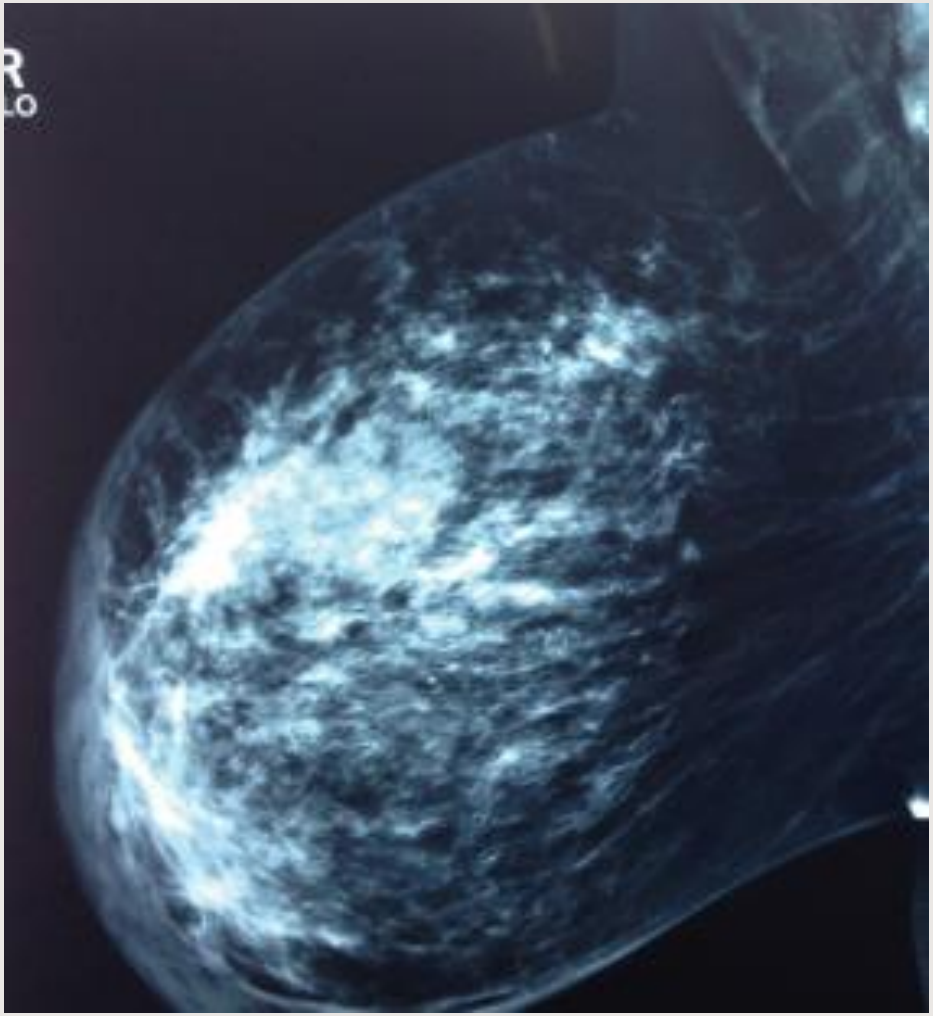
31 May 2013 (3.7 cm)

25 July 2013 (2.0 cm)

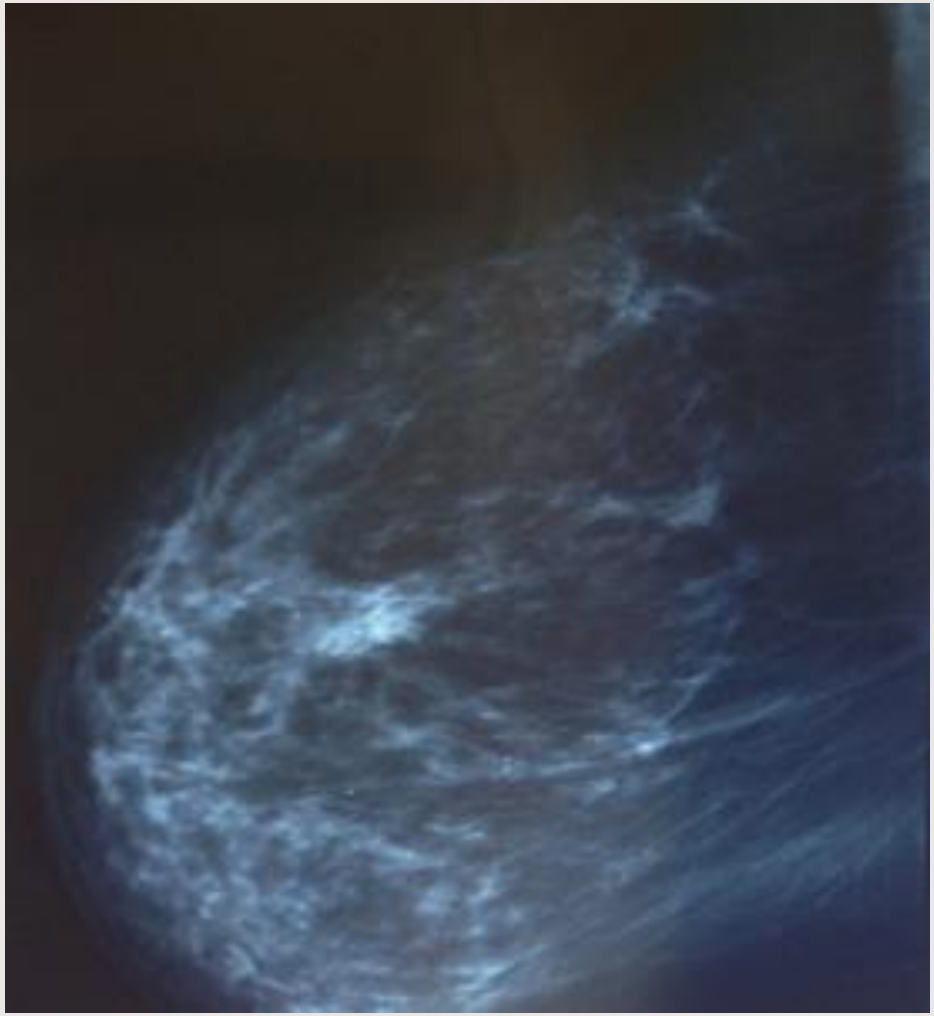


19 weeks

31 May 2013



October 2013



T + Letrozole implant
Side effects from chemotherapy

51 yo female diagnosed with 3.3 cm IDC

To receive pre-op chemotherapy

Testosterone (180 mg) + Letrozole (8 mg) implants

- 43% reduction in tumor at day 41, prior to starting CTX
- Complete pathological response
- No long term effects (cardiac or neurological) from CTX

Glaser, R. L., York, A. E., and Dimitrakakis, C. 2017. Subcutaneous testosterone-letrozole therapy before and concurrent with neoadjuvant breast chemotherapy: clinical response and therapeutic implications. Menopause. 24, 7, 859-864.

Cost

TABLE 1. *Cost of treatment in US dollars*

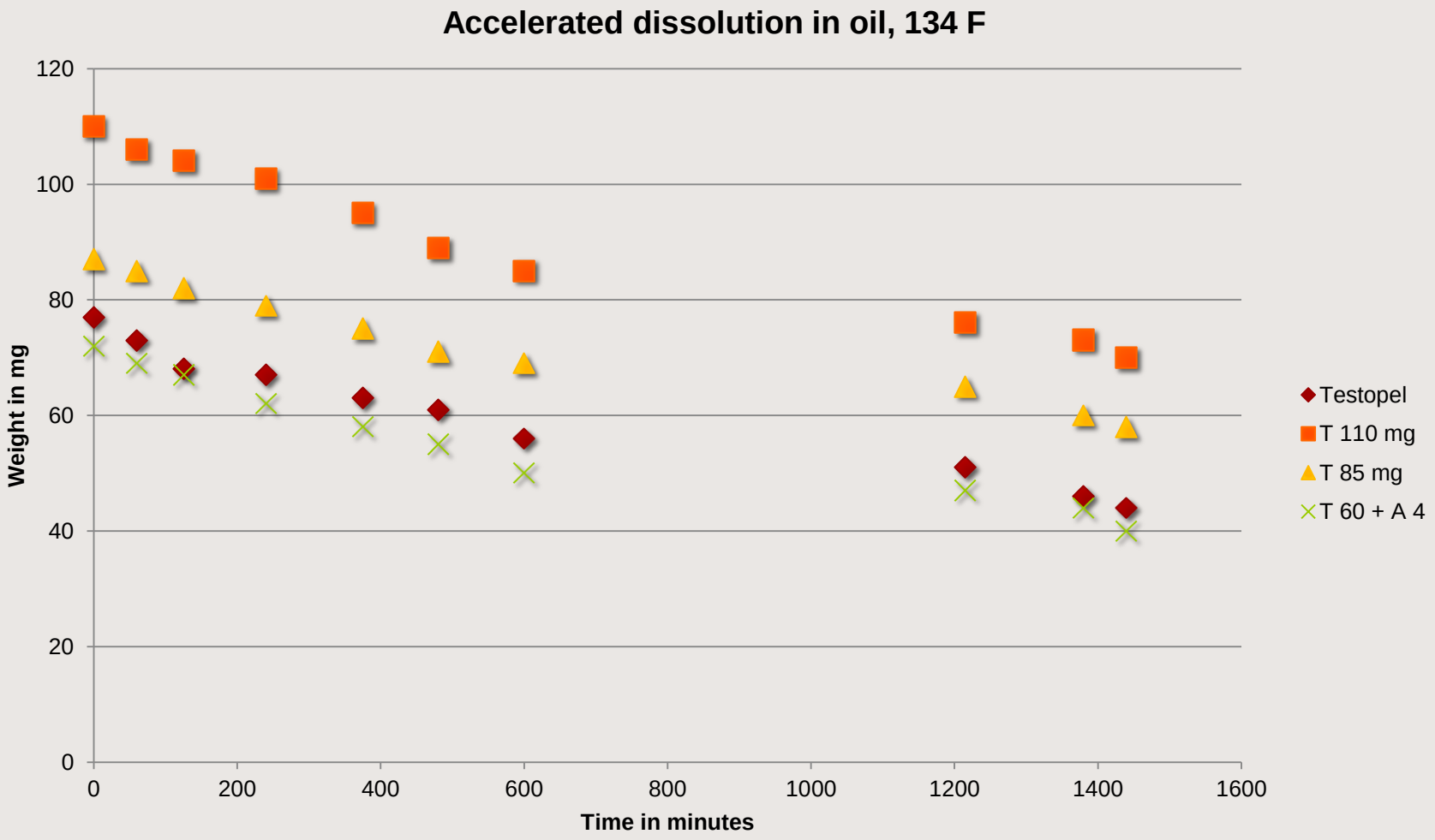
	Amount billed	Amount covered by insurance
T + AI implant	230[a]	0[b]
Chemotherapy (six cycles)	125,000	60,600
Six additional trastuzumab	46,500 (7,750 × 6)	22,590 (3,765 × 6)
Pegfilgrastim	46,200 (7,700 × 6)	23,400 (3,900 × 6)
Two-day hospital charge	71,000	61,420
Additional expenses[c] (estimate)	45,000	25,000

$230 includes office visit, insertion procedure, review labs, and medical care for 3 months.

RESEARCH & DATA

Efficacy and safety

In vitro dissolution studies



Efficacy in women

Glaser R, York AE, Dimitrakakis C. Beneficial effects of testosterone therapy in women measured by the validated Menopause Rating Scale (MRS). Maturitas. 2011;68:355-361.

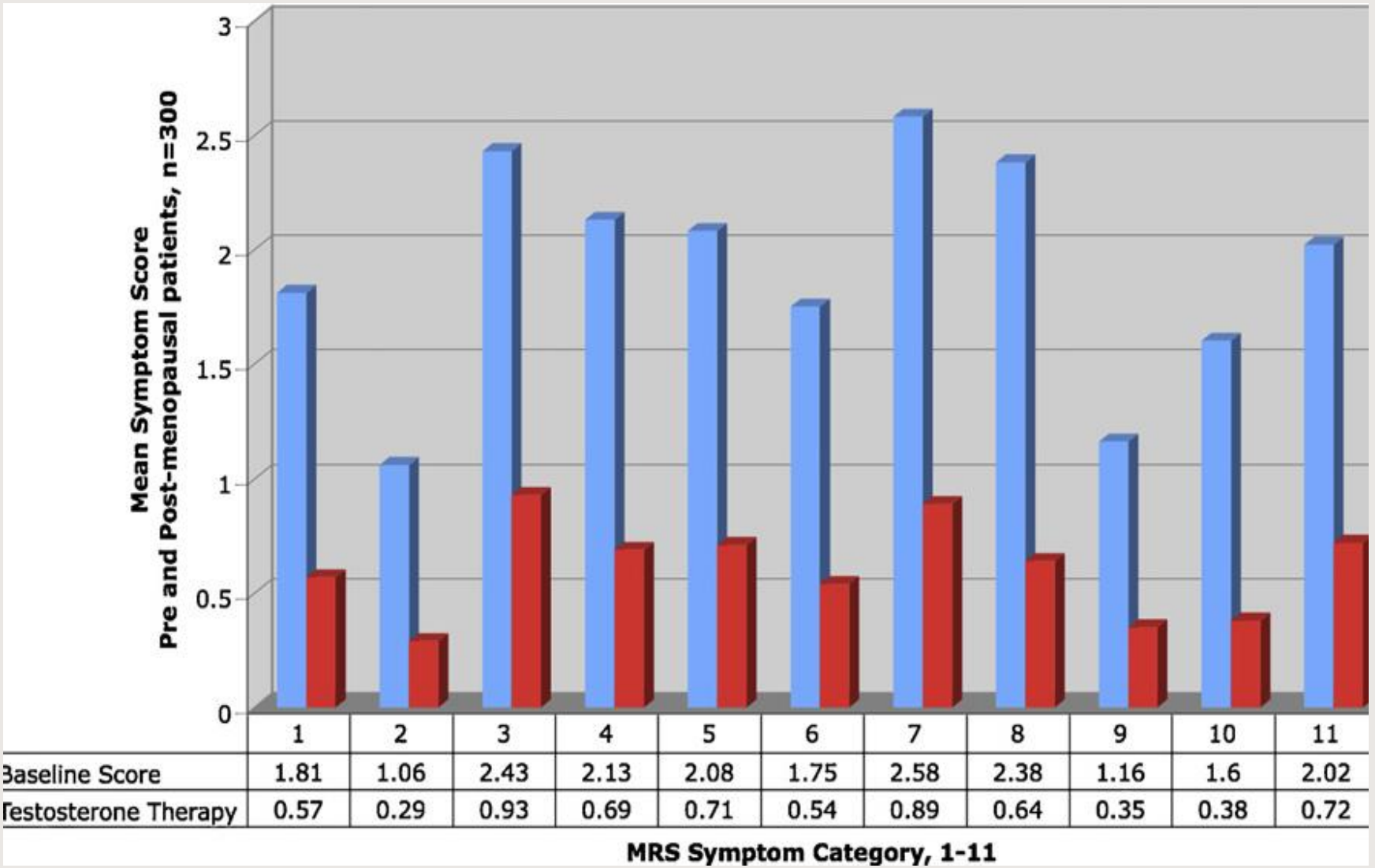
Testosterone implants alone (no estrogen)

N=300

108 premenopausal (35.3%)

Indications: T implants N=300 women, pre and post meno

Symptoms:	none	mild	moderate	severe	extremely severe
Score =	0	1	2	3	4
1. Hot flashes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐



	1	2	3	4	5	6	7	8	9	10	11
Baseline Score	1.81	1.06	2.43	2.13	2.08	1.75	2.58	2.38	1.16	1.6	2.02
Testosterone Therapy	0.57	0.29	0.93	0.69	0.71	0.54	0.89	0.64	0.35	0.38	0.72

Glaser, York, Dimitrakakis 2011

Migraine headaches-testosterone implants

Glaser R, Dimitrakakis C, Trimble N, Martin V. Testosterone pellet implants and migraine headaches: a pilot study. Maturitas. 2012;71:385-388.

	Combined cohort $N = 27$	Pre-menopausal $N = 16$	Post-menopausal $N = 11$
Mean age	47.4 ± 9.6 years	41.8 ± 5.5 years	55.5 ± 8.7 years
Mean severity score[a] at baseline	3.63 ± 0.55	3.72 ± 0.52	3.5 ± 0.59
Mean severity score[a] on therapy	0.37 ± 1.08	0.63 ± 1.36	0[b] ± 0
Absolute change[c] in severity score	3.26 ± 1.19	3.1 ± 1.46	3.5 ± 0.59
	$P < 0.001$	$P < 0.001$	$P < 0.001$

Voice changes

Prospectively followed 10 women treated with T pellet implants for one year

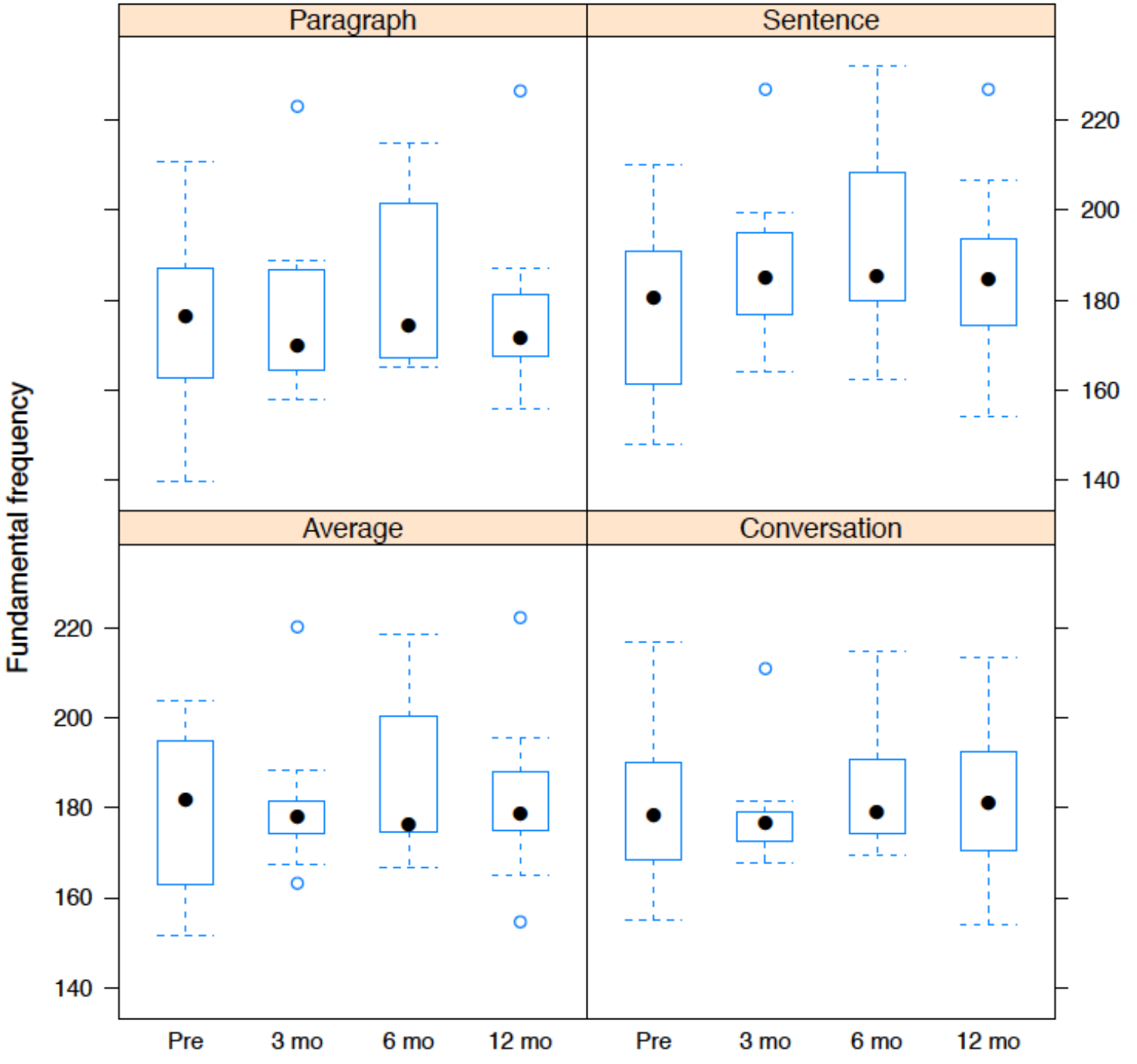
Mean T pellet dose 138.0 ± 22.7 mg

Measured fundamental frequencies at baseline, 3, 6, and 12 months

No change in fundamental frequency among subjects

FACT: **There is no evidence that SQ testosterone therapy causes hoarseness or irreversible vocal cord changes in women**

Glaser R, York A, Dimitrakakis C. Effect of testosterone therapy on the female voice. Climacteric. 2016;19:2;198.


Paragraph
Sentence
Average
Conversation
Fundamental frequency
140
160
180
200
220
Pre
3 mo
6 mo
12 mo

T is not excreted in breast milk

Testosterone, delivered by a subcutaneous pellet implant was effective in relieving symptoms of testosterone deficiency and was not measurably increased in breast milk or measurable in infant serum.

International Congress on Steroidal Hormones and Hormones & Cancer, Quebec City, Canada (September 2008)

Long term safety T implants

Glaser R, Dimitrakakis C. 58 BENEFICIAL EFFECTS OF SUBCUTANEOUS TESTOSTERONE THERAPY ON LIPID PROFILES IN WOMEN. Maturitas. 2012;71:S41.

Glaser RL, Dimitrakakis C. Reduced breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: a **prospective**, observational study. Maturitas. 2013;76:342-349.

Glaser, R. L., York, A. E., and Dimitrakakis, C. 2018. Abstract #1435/Poster presentation. Reduced incidence of breast cancer with testosterone implant therapy: a 10-year cohort study. 2018 San Antonio Breast Cancer Symposium. 2018, December: P6-13-02.

Over 60% reduction in the incidence of breast cancer

Safety of higher ‘male’ doses of T

- 500-1800 mg doses of T used to treat BCA patient
- Supra-physiologic doses in female to male transgender patients have been demonstrated to be safe

Research: Alliance cancer trial A221102

- National double-blind randomized trial
- Compounded combination T + A pellets
- Compounded topical cream
- Results under publication

Leon-Ferre, R, Le-Rademacher, J, Terstriep,S, Glaser, R. et.al. 2018. Abstract #1434/Poster presentation. A randomized, double-blind, placebo-controlled trial of testosterone (T) for aromatase inhibitor-induced arthralgias (AIA) in postmenopausal women: Alliance A221102. 2018 San Antonio Breast Cancer Symposium. 2018, December: P4-16-01

Pharmacokinetic studies

Glaser R, Kalantaridou S, Dimitrakakis C. Testosterone implants in women: pharmacological dosing for a physiologic effect. Maturitas. 2013;74:179-184.

Safety and efficacy of current T doses

Therapeutic levels on therapy

- Controversial ES guideline recommendation (not based on evidence)

  "… resulting in a mid-normal premenopausal value in a reference assay to avoid pharmacological T administration."

Pharmacologic dosing for a physiologic effect

Female study T implants

- Dose 133.3 ± 26.8 mg, range 55-240 mg
- Results

  Week 4 levels (n=154), **300 ± 107 ng/dl**

  4-6 x endogenous range, 44/72 ng/dl

  Symptoms returned (n=261), **171 ± 73 ng/dl**

  2-3 x endogenous range

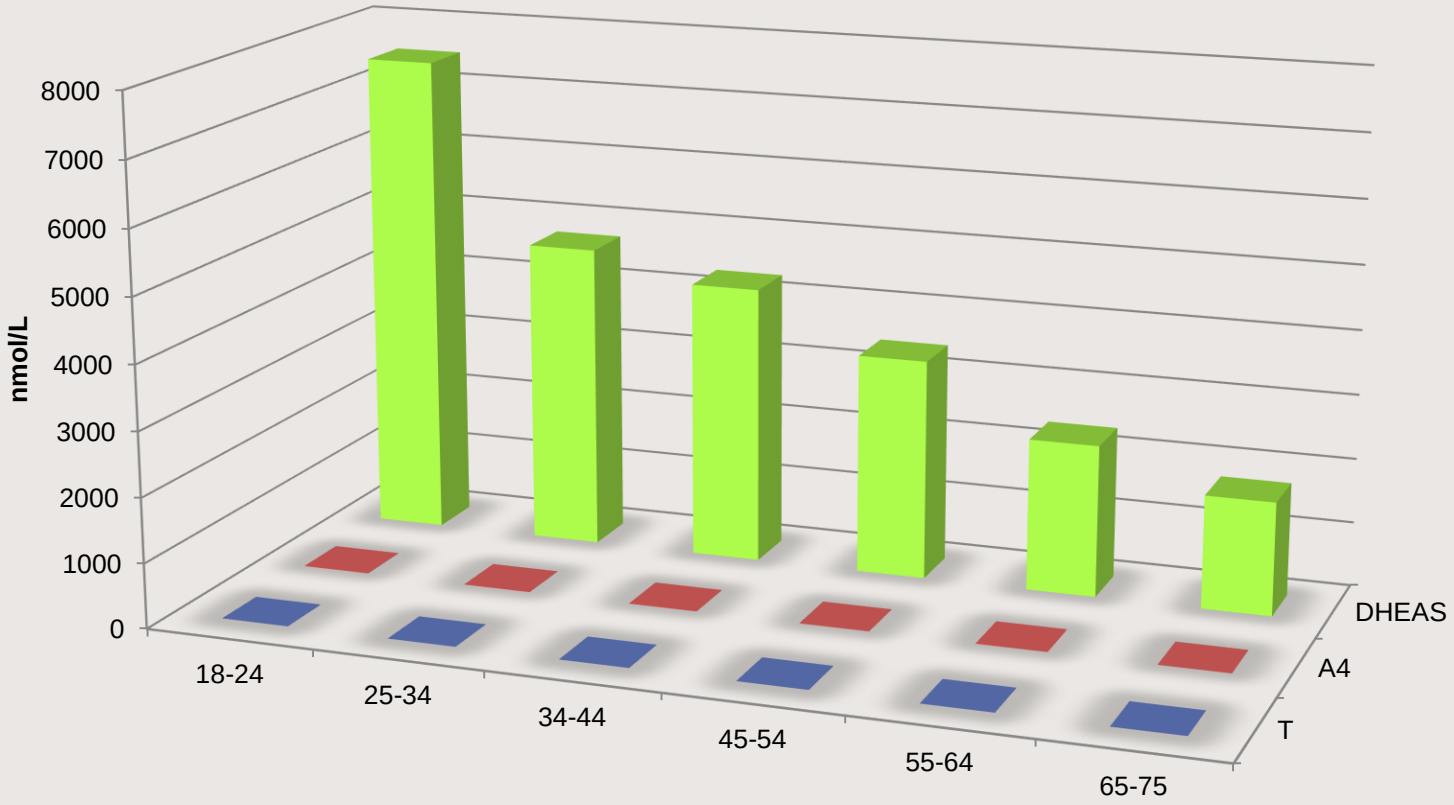
  Subset: Quest lab (n=154)

  TT 185 ng/dl (2-45 ng/dl)**, fT 19 pg/ml** (0.1-6.4 pg/ml)

  No ADE

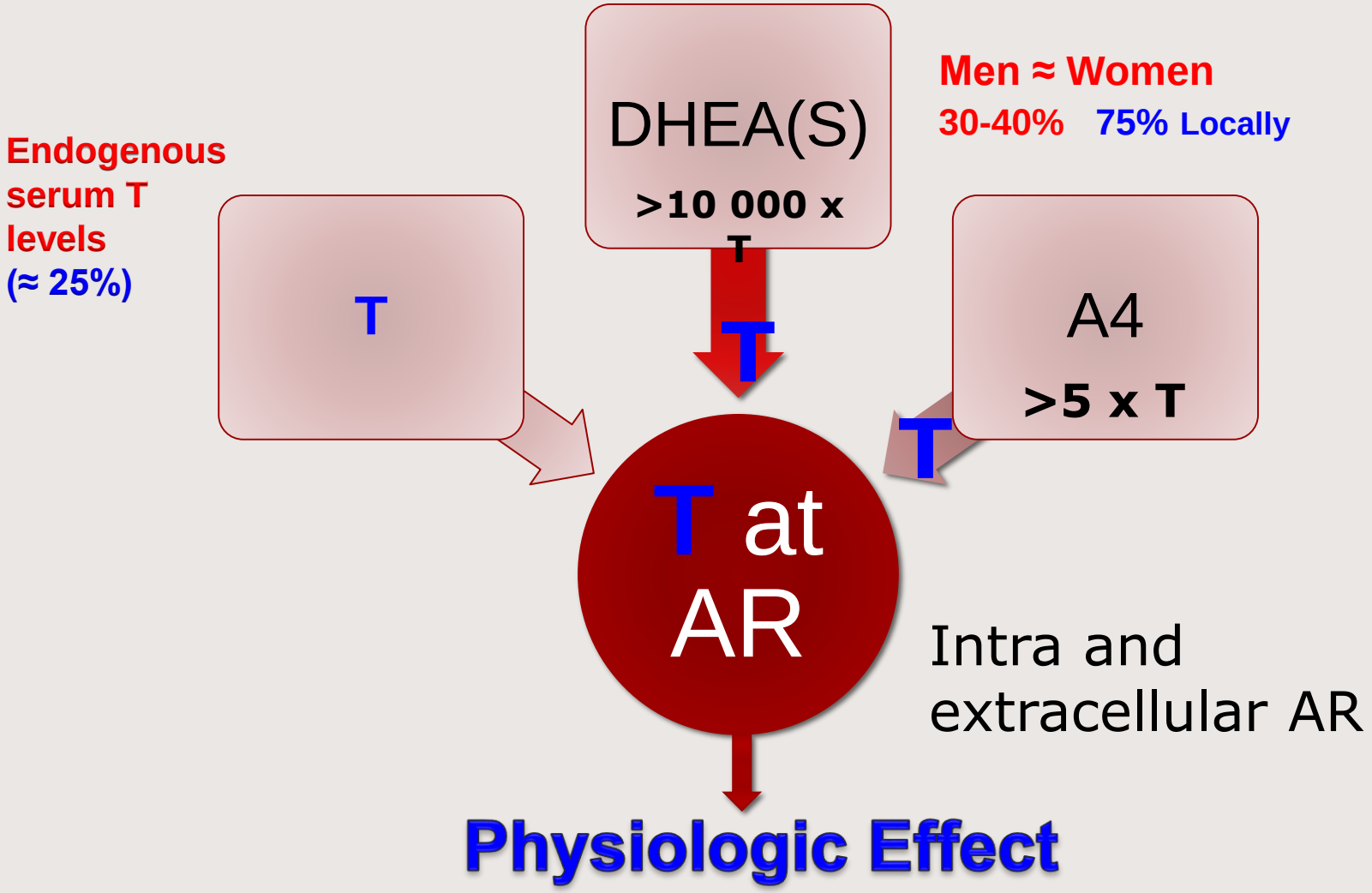
Glaser, R., Kalantaridou, S., and Dimitrakakis, C. 2013. Testosterone implants in women: pharmacological dosing for a physiologic effect. Maturitas. 74, 2, 179-184.

Basic physiology



3B-HSD (A4)➔17B-HSD (T)
17B-HSD (Adiol)➔3B-HSD (T)

T replacement at the end organ (cellular level)
Serum T + DHEA(S) + Androstenedione



Data

- Levels on therapy apply only to the SQ implant
- Basic physiology

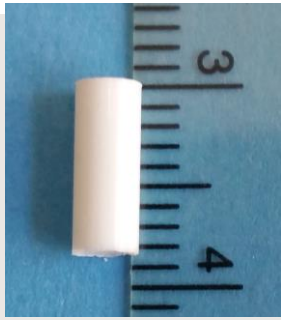
  Serum T levels reflect the contribution of androgen precursors to T available at the end organ

FACT: Symptoms returned T levels **171 ± 73 ng/dl**

TT 185 ng/dl (2-45 ng/dl)**, fT 19 pg/ml** (0.1-6.4 pg/ml)

FACT: **NO ADE** in over 10-years of therapy

Male data on compounded implants



- Glaser, R. L. 2017. Testosterone, anastrozole, and venous thrombosis. Maturitas. 103, 91. Presented at EMAS Amsterdam 2017

  SC T + A implant therapy does not increase and may lower the occurrence of venous thrombotic events.

- Subcutaneous Testosterone Anastrozole Therapy in Men: Rationale, Dosing, and Levels on Therapy (Under publication IJPC 2019)

  Low-dose anastrozole released from the combination implant maintained low estradiol levels throughout the implant cycle and prevented clinical side effects attributed to excess estrogen.

Myths and misconceptions

Glaser R, Dimitrakakis C. Testosterone therapy in women: Myths and misconceptions. Maturitas. 2013;74:230-234.

There is no data…. The biggest myth of all

CONCLUSION

Compounded testosterone use in women 2019

Conclusion

- T is critical for health, and well-being
- The gradual decline of T associated with aging is responsible for many of the adverse signs and symptoms of aging including mental and physical deterioration
- TRT must be done with adequate doses

  Clinical effect (benefits) vs. adverse events (risks)

  -Not serum levels on therapy

Compounded hormones

- Compounded hormones are critical to the care of millions of breast cancer patients in whom estrogen therapy is contraindicated
- Compounded T + AI (anastrozole/letrozole) implants have been shown to treat breast cancers and improve QoL in breast cancer survivors

  Maintain therapeutic T levels without raising estradiol levels
- Compounded T + A implants prevent side effects of of excess estrogen in male and female patients

Compounded testosterone

- Compounded testosterone implants have been safely used in women for over 80 years
- Subcutaneous testosterone is clinically effective
- Data exists on the safety, efficacy, and pharmacokinetics of compounded subcutaneous testosterone implants
- There is a demand (over 80 years)
- Supply: FDA approval in women????
- There will still be a need for compounding!
  - Dosing
  - Inactive ingredients
  - Combination formulations

The Art of Medicine

HORMONE LEVELS

To measure or not to measure

Critics of compounded BHRT

- Under-dosing or overdosing

  Can occur with compounded BHRT or conventional HT

- Measuring levels on therapy is controversial

  Ranges on (T) therapy are controversial but data supports efficacy and safety

- Equivalence studies

  No two patients absorb, distribute, metabolize, or excrete any medication the same

Clinical decision vs. labs

Hormone levels fluctuate and are unreliable.

Standard of care: an individual patient should be treated based on his/her symptoms, response to therapy, as well as the benefits and risks of therapy.

An individual's physical comfort may not be related to their absolute hormone levels.

Sherif K, Sherif K. Medical Association Guidelines, Post-2002/Women's Health Initiative Findings. Hormone Therapy: A Clinical Handbook. 2013;21-3

Known

Testosterone’s effect is dose dependent

Controversy: T levels on therapy (ES)

"Clinicians should maintain serum T levels during treatment in the mid-normal range for healthy young men".

"… resulting in a mid-normal premenopausal value in a reference assay to avoid pharmacological T administration."

NO EVIDENCE that this is effective therapy or that higher levels are associated with ADE

Do not specify method of delivery

The data disagrees

Physiology disagrees

Clinically effect dose, No ADE

Year published	Study	Mean T dose mg.	Mean serum T ng/dL
2013	PK N=154 (4 week) N=261 (end)	133.3 ± 26.8	300 ± 107 171 ± 73
2014	Breast Cancer N=73	168.9 ± 32.2	354 ± 149
2016	Voice Study N=10	138.0 ± 22.7	472 ± 148

Weight/BMI and levels on therapy

Week 1 levels women (preliminary data), Male data

- Levels on therapy affected by weight/BMI
- Women < 130 pounds have higher levels on therapy despite lower (weight based) dosing

  Wt < 130 542.3 ± 223.7 ng/dl (mean dose 165 mg)

  Wt > 160 452.5 ± 192.5 ng/dl (mean dose 213 mg)

- Similar results in male patients (under publication IJPC)

  The mean T level when symptoms return in men with a BMI <25 is 650.5 ng/dl compared to 586.4 (BMI 25-<30), 567.9 ng/dl (BMI 30-<35), and 514.7 ng/dl (BMI ≥35).

  Midrange when symptoms return

Micromanaging T levels

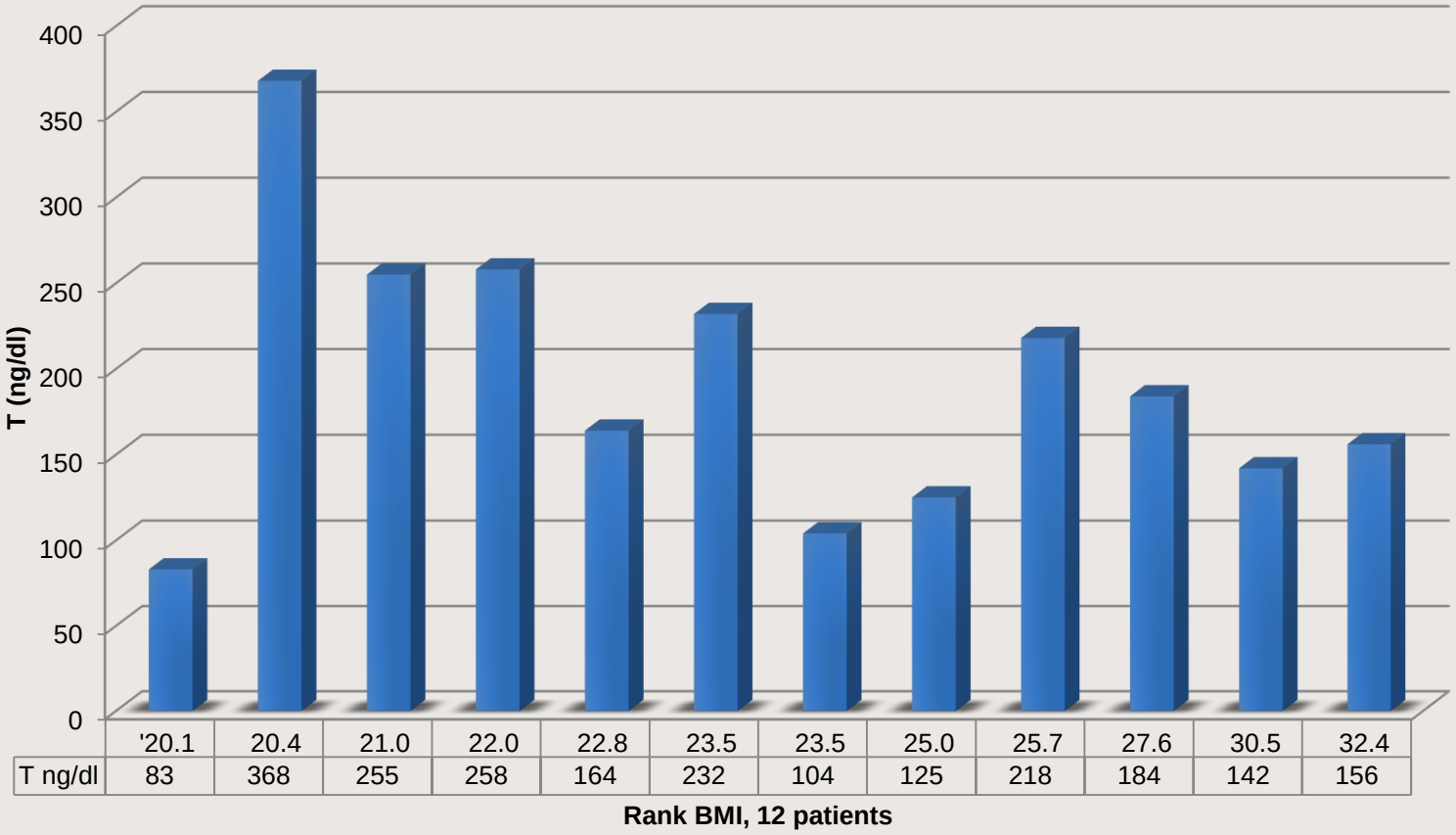
- Reliability
- Inter-individual variation
- Intra-individual variation

Therapy should be based on clinical effect and therapeutic response (benefits) vs. side effects (risks)

Inadequate doses are ineffective

Inter-individual variation

Week 4 serum T levels, 100 mg T implant N=12



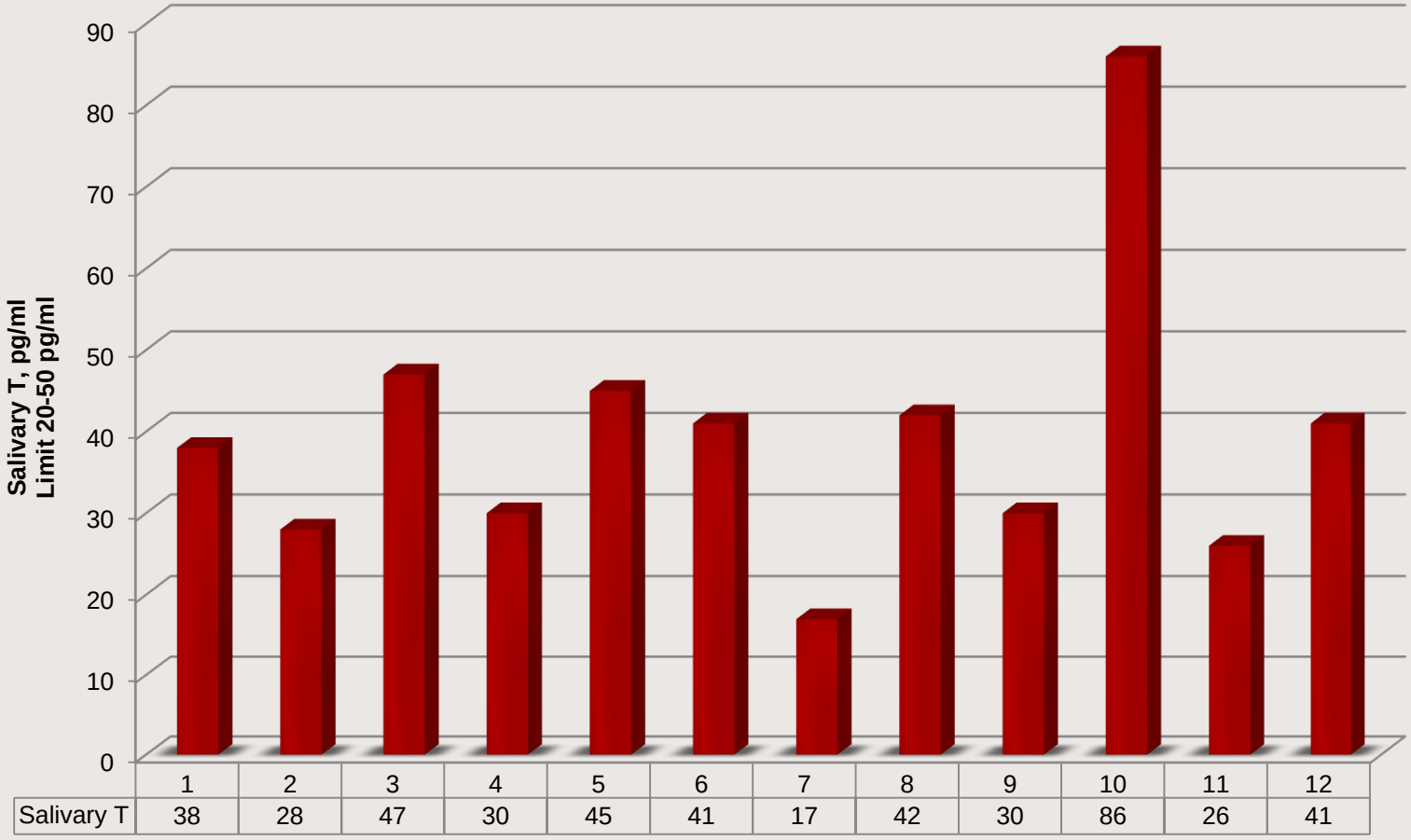
	'20.1	20.4	21.0	22.0	22.8	23.5	23.5	25.0	25.7	27.6	30.5	32.4
T ng/dl	83	368	255	258	164	232	104	125	218	184	142	156

Rank BMI, 12 patients

Mean T level 190.8 ± 80 ng/dl (range 83-368, CV 41.9%) Zava, Glaser

Method of testing

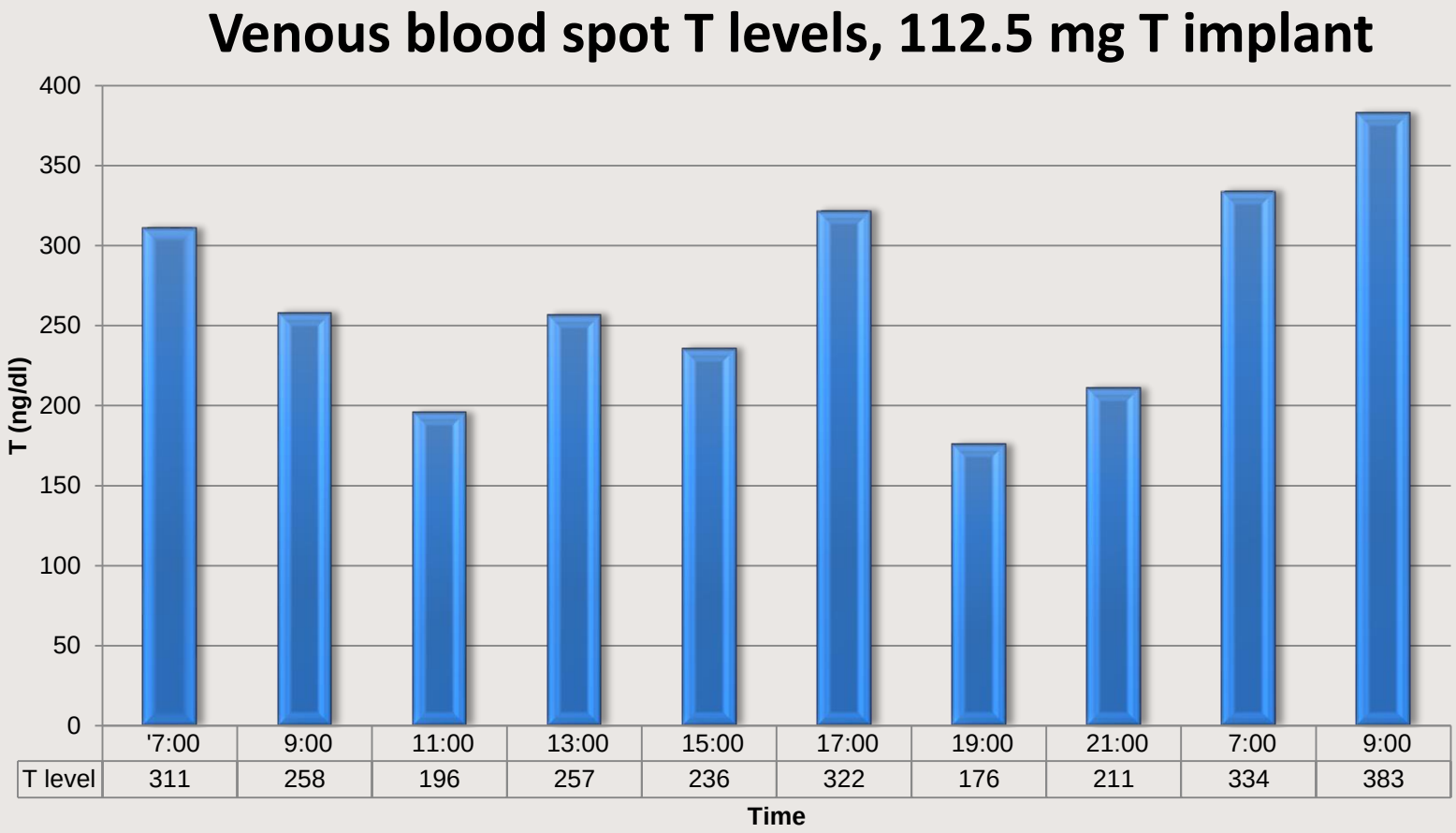
Salivary T levels, week 4, 100 mg T implant



	1	2	3	4	5	6	7	8	9	10	11	12
Salivary T	38	28	47	30	45	41	17	42	30	86	26	41

Mean 39.3 ± 17.2 pg/ml (range 17-86, CV 43.8%). Ref. 20-50 pg/ml (Zava, Glaser)

Intra-individual variation
Single female patient tested over 26 h



Mean T level 268.4 ± 67.1 ng/dl (range 176-383, CV 25%) Zava, Glaser

ACOG Committee Opinion No. 532

Hormone level testing

- (However) individualized testing in only indicated when a narrow therapeutic window exists for a drug or drug class
- Steroid hormones… do not meet these criteria and thus do not require individualized testing.

ACOG Hormone level testing cont.

- If treatment is initiated for symptom control, subjective improvement in symptoms is the therapeutic end point, and there is no need to assess hormone levels.
- Hormone therapy should not be titrated to hormone levels.

AGREED!

Compounded Bioidentical Hormones in Endocrinology Practice: An Endocrine Society Scientific Statement JCEM 2016

… there is no evidence that monitoring compounded HT with serial salivary or blood testing is effective, except in the case of thyroid hormone.

Idiom*

We continue to recommend against making a diagnosis of androgen deficiency syndrome in healthy women because there is a lack of a well-defined syndrome, and data correlating androgen levels with specific signs or symptoms are unavailable.

Versus

…recommend that HT be individualized on the basis of symptoms (not hormone levels)

**Idiom- Speaking/maintaining contradictory positions or beliefs, often self-serving*

Androgen Therapy in Women: A Reappraisal:
An Endocrine Society Clinical Practice Guideline JCEM 2014

Labrie 17

- Serum testosterone is not a valid marker of androgenic activity in women
- ...it is not surprising that despite long series of prospective and case-control cohort studies performed during the last 30 years, a correlation between serum testosterone and any clinical condition believed to be under androgenic control in women has remained elusive.

Recommend testing for T JCEM 2014

- 5.2 If a woman is to be given a trial of T therapy, we suggest checking baseline T level and the use of an approved non-oral preparation for women (such as a transdermal patch, gel, or cream) if such a treatment is available
- 5.3 We suggest monitoring T levels 3–6 weeks after initiation of therapy *and* every 6 months thereafter to assess for patient overuse or signs of androgen excess

No evidence

Confused???

- …baseline hormone measurements to replace “abnormal” hormone deficiencies has no basis in medical practice.

- …HT be individualized on the basis of symptoms (not hormone levels) for menopausal women using HT with estrogen and/or progestin, or androgen.

Convictions are more dangerous enemies of truths than lies.

Friedrich Nietzsche

THE INDUSTRY

Specialty societies and COI

Testopel® 75 mg pellet	$92.30 per 75 mg pellet *92.30	$2215.20 for 1800 mg dose (male)	**$18.46**/day based on 120 d cycle	
Compounded Testosterone pellet JJ	$15 per 100 mg pellet	$270 for 1800 mg dose (male) $30-45 (female) dose (2-3 pellets)	**$2.25**/day based on 120 d cycle $0.50/day female 90 d cycle	88% less
Androgel® 88 g of 1.6%	$625 vs. **Generic** $241.25 (coupon)	40.5 mg/2 pumps in 5.0 g gel	**$20.85**/d **$8.04**/d generic	
Compounded Testosterone gel Or cream WIP	**Gel** 40 mg/g $72/30 d **Cream** 160 mg/g $35/30 d $91/90 d	80 mg dose 80 mg dose 0.5 g per day	**$2.40**/day **$1.17**/day $1.01/day, 90 d supply	70% less than generic 85% less than generic >95% AndroG
Bijuva® Oral capsule E2/P	$238.98 one month (#30) $7.96	One per day	**$7.96**	
Compounded Oral capsule E2/P WIP	$39.60 (#30) $1.32 (#30) $1.14 (#90)	One per day	**$1.14**-1.31	85% less
Estrogel® Topical E2 gel	$106.88-149.95 per 50 gram bottle $3.00/gram without coupon	1.25 gm /pump* (0.75 mg E2) 2 pumps per day	≈ $3.75/1 pump **$7.50** for 1.5 mg E2 (2 pumps)	
Compounded Topical E2 gel WIP	$50 per 50 gram bottle $1.00/gram	1 to 1.5 gram depending on mg E2/gm gel	**$1.00 - $1.50**	Over 50-80% less

Specialty societies (funded)

ES, NAMS, ACOG, IMS

- Opinions
- Guidelines
- Journals
- COI
- KOL
- Meetings
- Presentations

Competition

- Most articles, guidelines, and opinions expressing concern over compounded BHRT are sponsored by pharmaceutical companies (specialty societies)
- Published in ‘Society’ Journals
- Physician authors with COI
- Ghost authors or paid marketing authors (e.g. Precise publications, LLC)

COI Compounded hormones ES 2016

JCEM

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2013 The following JCEM Editors reported relevant financial relationships:

The Editor-in-Chief, Leonard Wartofsky, M.D., is a Consultant for Asurogen, Genzyme, and IBSA, and is on the Speaker's Bureau for Genzyme. **Kenneth Burman, M.D.,** is a Consultant for Medscape and UpToDate; a Reviewer for the Endocrine Fellows Foundation; and has received Institutional Grants for Research from Amgen, Eisei, and Pfizer. **Samuel Dagogo-Jack, M.D.,** is a Consultant for Merck and Novo Nordisk; a Grantee for the American Diabetes Association, AstraZeneca, Boehringer Ingelheim, National Institutes of Health, and Novo Nordisk; and a Grant Reviewer for the American Diabetes Association and National Institutes of Health. **Silvio Inzucchi, M.D.,** is a Consultant/Advisor for Boehringer Ingelheim, Genentech, Janssen, Merck, and Takeda; has DSMB Activity with Amgen, Esai, and Gilead; and receives CME support from Abbott, Amylin, Boeringher-Ingelheim, Merck, and Takeda. **Kieren Mather, M.D.,** received an Investigator-initiated Grant from Novo Nordisk. **Lynnette Nieman, M.D.,** is an Author/Editor for UpToDate, and receives Research Support from HRA-Pharmaceutical.

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‘Classic faux-advocacy’

- The Hormone Health Network offers a variety of programs and services to reach the **public** with important hormone-related information. Its strategies involve dissemination and promotion directly to consumers, physicians and consumer media. HHN welcomes the opportunity to **collaborate with corporations**, patient support groups, government agencies, and non-profit organizations **to expand the reach of important health messages in creative ways.**

Articles

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Published Online October 3, 2006

DISCLAIMER: Clinical Practice Guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of healthcare providers and each patient's individual circumstances.

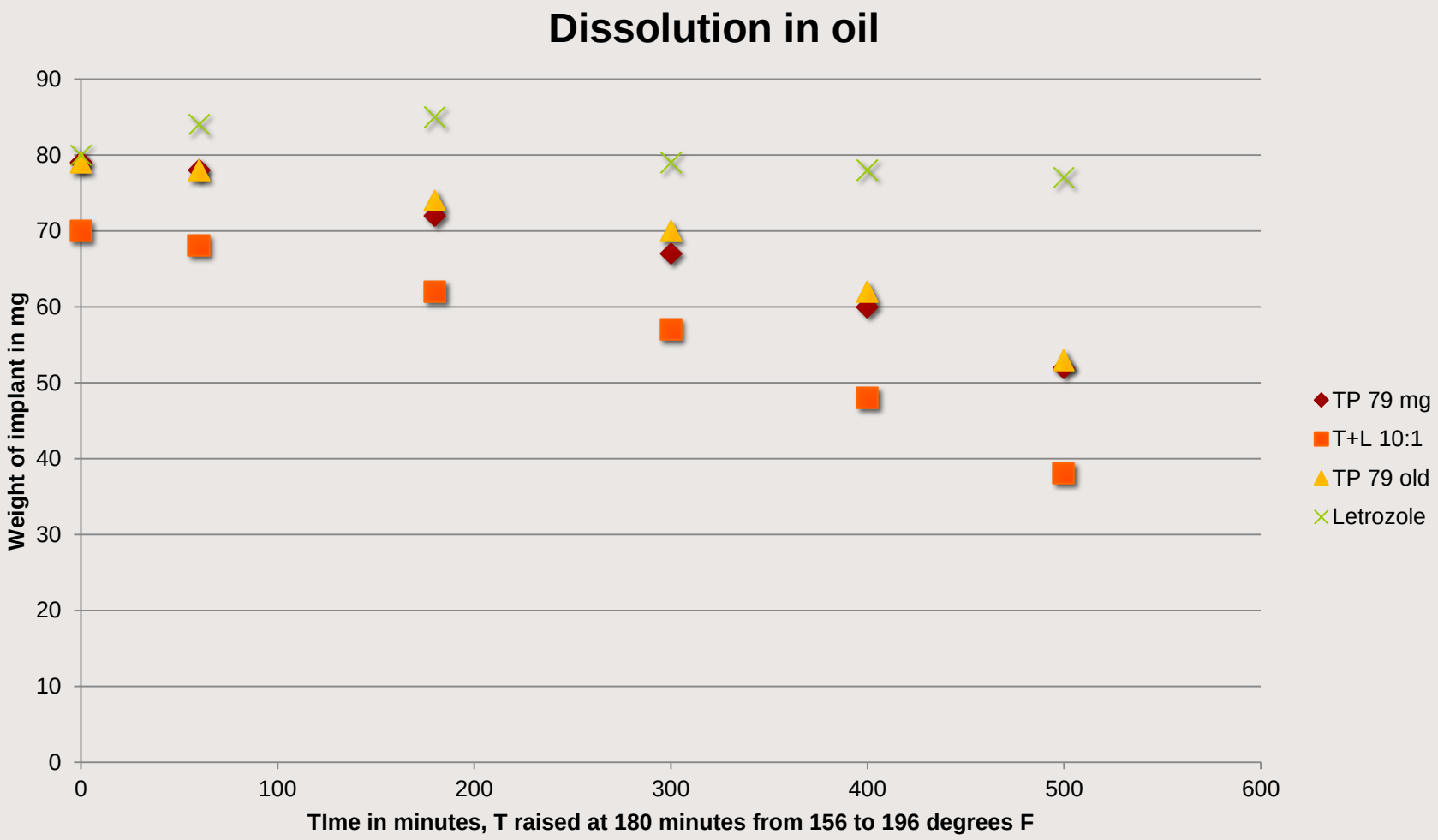
COMPOUNDING BHRT

Issues and controversies

Compounding

- False claims of superiority, proprietary pellets
- Some pharmacies compound formulations without testing
  - Anastrozole alone implant
- Omit autoclaving pellet, which heat fuses the implant and slows release. BUT, this has been dictated by some state boards of pharmacy.
  - Have not done dissolution testing
  - Gamma radiation may be acceptable
  - The FDA approved pellet is autoclaved and the process has worked for over 80 years.

Testing omitted



Against the routine use of estradiol pellets

- Not a compounding issue
- Physician decision

- Not needed
- T is the major source of estradiol at the cellular level
- Continuous T provides adequate estradiol in the majority of women
- Complications

Estradiol pellet

- Estradiol can accumulate
- Prolonged stimulation of the uterine lining (prolonged bleeding)
- Increased risk of breast with higher doses MWS 03

  Not removable (Treat with Tamoxifen)
- No evidence to support dosing to suppress FSH
- No evidence to support ‘minimum’ serum levels of E2

- Most physicians prescribe lower doses of E2 (6-15 mg)

  Limited data, safer
- Estra pellet FDA approved for shipping overseas

Data does exist (Studd 94)

	Oestradiol implants		
	25 mg	50 mg	75 mg
Oestradiol (pmol/l)	327 (114–853)	358 (220–957)	518 (167–828)
FSH (iu/l)	26·8 (2–66)	11·6 (1·1–28)	5·55 (0·9–33·7)

References
PK compounded estradiol implants

Stanczyk FZ, Shoupe D, Nunez V, Macias-Gonzales P, Vijod MA, Lobo RA. A randomized comparison of nonoral estradiol delivery in postmenopausal women. Am J Obstet Gynecol. 1988;159:1540-1546.

Lobo RA, March CM, Goebelsmann U, Krauss RM, Mishell DR. Subdermal estradiol pellets following hysterectomy and oophorectomy. Effect upon serum estrone, estradiol, luteinizing hormone, follicle-stimulating hormone, corticosteroid binding globulin-binding capacity, testosterone-estradiol binding globulin-binding capacity, lipids, and hot flushes. Am J Obstet Gynecol. 1980;138:714-719.

Studd JW, Holland EF, Leather AT, Smith RN. The dose-response of percutaneous oestradiol implants on the skeletons of postmenopausal women. Br J Obstet Gynaecol. 1994;101:787-791.

Comparison-equivalence

Formulation	Dose (mg)	Serum level (pg/ml)
CEE	0.625 1.25	40 60
Micronized estradiol	1 2	40 60
Transdermal estradiol patch	0.05 0.10	25-40 60
Estradiol gel	1	50
Estradiol implant	25	89

Estrogen formulations and serum levels

Randomized trial

- Compounded OMP 100 mg vs. Prometrium (100 mg)

  Serum progesterone levels were comparable in conventional vs. compounded groups

  Prometrium #30, $328.88 with coupon

  Generic #30, $22.75 with coupon

  Compounded #30, $39.50

- Topical BiEst, estradiol levels were not equivalent to the patch

Sood R, Warndahl RA, Schroeder DR et al. Bioidentical compounded hormones: a pharmacokinetic evaluation in a randomized clinical trial. Maturitas. 2013;74:375-382.

Critics of cBHRT

- Under-dosing or overdosing

  Can occur with compounded BHRT or conventional HT

- Measuring levels on therapy is controversial

  Ranges on (T) therapy are controversial but data supports efficacy and safety

- Equivalence

  No two patients absorb, distribute, metabolize, or excrete any medication the same

Standard of care: an individual patient should be treated based on his/her symptoms, response to therapy, as well as the benefits and risks of therapy

BHRT ‘movement’

- Popularity
- Marketing
- Hype and claims
- Micromanaging dosing based on repetitive testing
  - No data
- Self appointed experts and their methodology
  - Data often only case presentations
  - Unsubstantiated claims of superiority
  - Unsubstantiated criticism of other therapies (blogs etc.)
- Lack of data on some preparations
  - Safety is not an issue (excluding higher doses of estradiol)

Separate ‘compounding’ from ‘BHRT movement’

Ideology is here to stay

- Individualized therapy
- Listening to the patient
- Bio-similar formulations (advantage)

There will always be a need for compounded BHRT

You have your way.

I have my way.

As for the right way, the correct way, and the only way,

it does not exist.

Friedrich Nietzsche