Beyond Testosterone: Exploring Alternative Therapies For Low T

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Introduction

- Testosterone replacement (TREP) therapy is the only FDA approved treatment for hypogonadism .

- Three widely publicized studies (two large retrospective studies and one small prospective) have brought into doubt the cardiovascular safety of TREP despite prior studies suggesting that TREP might be beneficial to the cardiovascular system

Research article | Open access |
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Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials

Outcome of the study

- The effects of testosterone on cardiovascular-related events varied with source of funding.

- Nevertheless, overall and particularly in trials not funded by the pharmaceutical industry, exogenous testosterone increased the risk of cardiovascular-related events, with corresponding implications for the use of testosterone therapy.

Research

Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

Outcome of the study

- Among a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes.

- These findings may inform the discussion about the potential risks of testosterone therapy.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adverse Events Associated with Testosterone Administration

Shehzad Basaria, M.D., Andrea D. Coviello, M.D., Thomas G. Travison, Ph.D., Thomas W.

Outcome of the study

- In this population of older men with limitations in mobility and a high prevalence of chronic disease, the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events.

- The small size of the trial and the unique population prevent broader inferences from being made about the safety of testosterone therapy.

- Exogenous testosterone replacement leads to negative feedback on the hypothalamic–pituitary-gonadal (HPG) axis, causing suppression of endogenous testosterone production and spermatogenesis.

- Other side effects are increase prostate specific antigens(PSA) changed lipid serum, polycythaemia and gynecomastia.

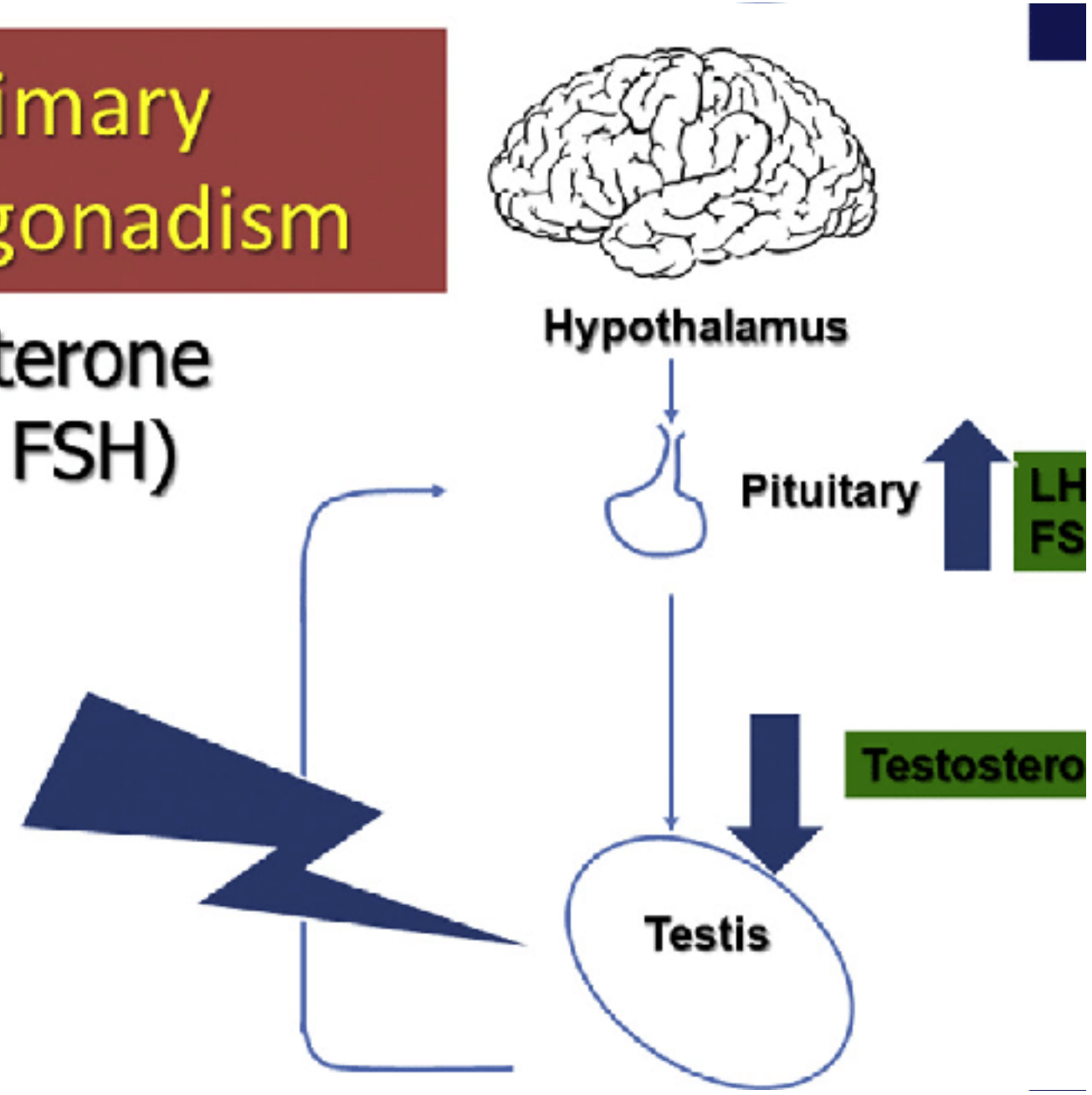
"I stopped taking the medicine because I prefer the original disease to the side effects."

TREP

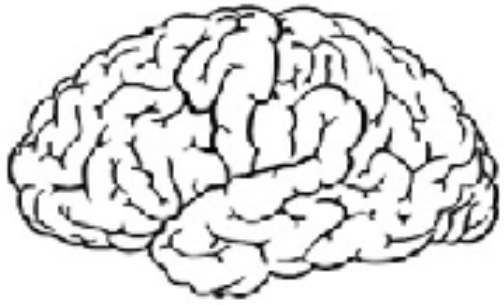
TRES

Primary Hypogonadism

↓Testosterone
↑ LH (± FSH)



Secondary Hypogonadism



Hypothalamus

Pituitary

LH
FSH

↓Testosterone
↓LH (± FSH)

Testosterone

Testis

Alternative of testosterone

- Life Style Modification
- GnRH Agonists
- Human chorionic gonadotropins
- Selective Estrogen Receptors Modulators (SERMs)
- Aromatase Inhibitors
- Stem cell therapy

Lifestyle modification

- Lifestyle changes can have a significant impact on testosterone levels.
- Ensuring a balanced and nutritious diet, engaging in regular exercise, managing stress, and getting adequate sleep can all contribute to optimizing testosterone levels naturally.
- While lifestyle modifications may not provide drastic increases in testosterone production, they can help improve symptoms and overall well-being.

Diet

1. Dietary choices can increase testosterone levels in the body. Some dietary factors that can help boost testosterone levels:
2. Adequate protein intake: Consuming enough protein, especially from sources like lean meats, fish, eggs, and legumes, can support testosterone production.
3. Healthy fats: Including healthy fats in your diet, such as avocados, nuts, seeds, and olive oil, can provide the necessary building blocks for testosterone synthesis.

3. Vitamin D: Adequate levels of vitamin D are crucial for testosterone production. Foods high in vitamin D include fatty fish (salmon, mackerel, and trout), fortified dairy products, and eggs.
4. Zinc: Zinc is an essential mineral needed for testosterone production. Foods rich in zinc include oysters, red meat, poultry, beans, and nuts.
5. Magnesium: Magnesium plays a role in regulating testosterone levels. Foods rich in magnesium include dark leafy greens, whole grains, nuts, and seeds.
6. Adequate calorie intake: Eating enough calories to support healthy hormone production is important. Extreme caloric restriction or low-calorie diets can lower testosterone levels. It's essential to maintain a well-balanced and nutrient-rich diet to support optimal testosterone levels.

Exercise

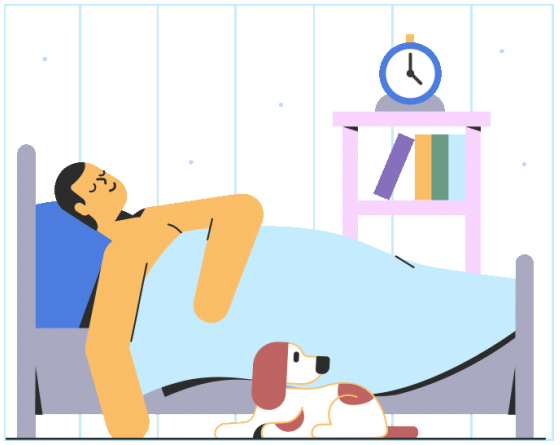
- Exercise can increase testosterone levels in the body.
- Studies have shown that engaging in high-intensity resistance training, such as weightlifting or interval training, can lead to an increase in testosterone production.
- Regular exercise and physical activity have been found to contribute to overall hormonal balance in the body.

Weight loss

- lifestyle modification program involving aerobic exercise and diet modification significantly increased mean testosterone levels

- Individuals who lost ≥10% of weight showed a significant increase in testosterone levels

Improvements in sleep



- Improvements in sleep quality and duration can positively affect serum testosterone levels and can provide an additional medication-free alternative to TREP.

- Sleep deprivation (restriction of sleep to 5 hours a night) decreased testosterone levels by 10% to 15%.

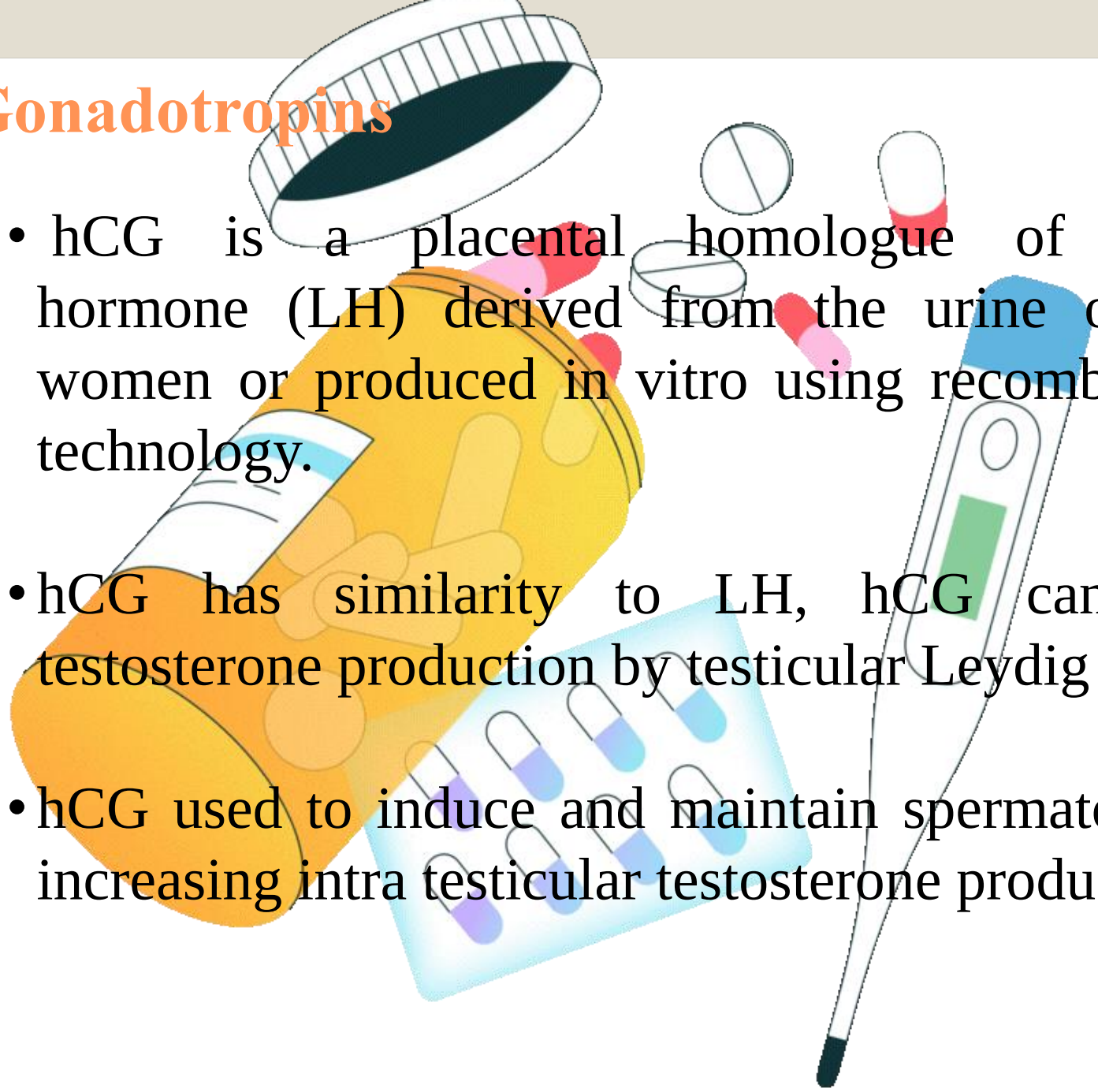
Decreasing Stress

- Stress is the major contributor to hormonal imbalance.
- Chronic stress can lead to increased cortisol levels, which can interfere with testosterone production.
- Managing stress through practices such as meditation, exercise and adequate sleep can help restore hormonal balance.

GnRH Agonists

- Pulsatile GnRH treatment has been used to restore fertility in patients with central hypogonadism with intact pituitary function.
- GnRH therapy must be administered in a pulsatile manner by a subcutaneous pump every 2 hours.
- Pulsatile GnRH therapy is expensive and requires experience and specific pump material.
- Outcome of GnRH therapy and therapy with gonadotropins is similar.
- GnRH is no longer used in routine clinical practice.

Gonadotropins



- hCG is a placental homologue of luteinizing hormone (LH) derived from the urine of pregnant women or produced in vitro using recombinant DNA technology.
- hCG has similarity to LH, hCG can stimulate testosterone production by testicular Leydig cells.
- hCG used to induce and maintain spermatogenesis by increasing intra testicular testosterone production.

Advantage of hCG over Testosterone

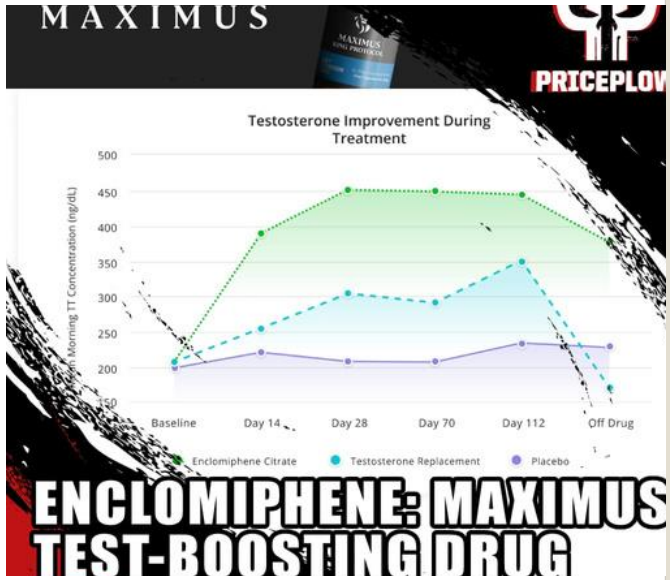
- The stimulation of testicular growth
- The greater stability of testosterone levels and fewer fluctuation in hypogonadal symptoms.
- Stimulating enough intra testicular testosterone to allow the initiation of spermatogenesis.

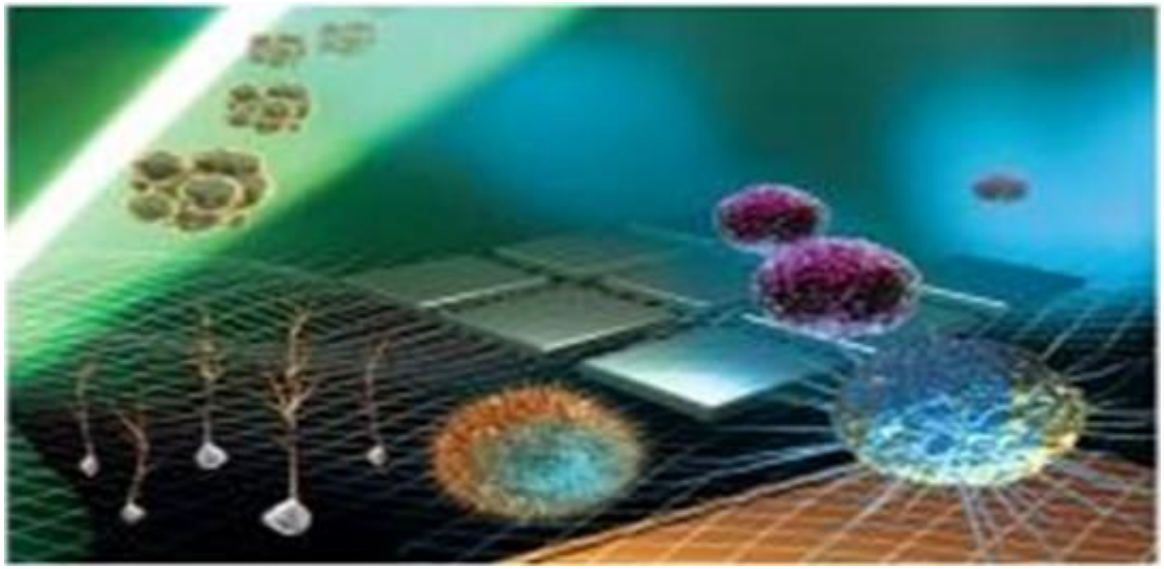
Aromatase Inhibitors

- AIs block the conversion of testosterone to estradiol by inhibiting the aromatase enzyme.
- AIs inhibition lowers estradiol levels and inhibits the negative feedback of estradiol on the hypothalamic-pituitary- gonadal axis.
- Inhibition of aromatase enzyme increases gonadotropin-releasing hormone, LH, and follicle-stimulating hormone levels, subsequently increasing serum testosterone levels.
- Anastrozole, Letrozole

Selective Estrogen Receptor Modulator

- SERMs has antagonistic effects on the estrogen receptors in the hypothalamus and the pituitary thereby increasing endogenous gonadotropin-releasing hormones (GnRH), LH and follicle-stimulating hormone (FSH).
- Increased endogenous gonadotropin levels which stimulate testosterone production.
- Clomiphene, Enclomiphene and tamoxifen





Stem Cell therapy

Stem Cell therapy

- Stem-cell-based therapy, in which a cell lineage can be re-established in human bodies to produce testosterone normally, would be the ideal choice for treating primary hypogonadism.

- Stem Leydig cells, mesenchymal stromal cells, pluripotent stem cells and fibroblasts are newly discovered sources of Leydig cells.

- Stem-cell-derived Leydig cells have many potential applications, including understanding the underlying mechanisms of primary hypogonadism, treating primary hypogonadism using transplantation therapy, and discovering drugs aimed at recovering Leydig cell function.

- Research is needed in the applications of Leydig cells, including constructing 3D testicular organoids, promoting in vitro culture conditions of Leydig cells, and exploring the in vivo transplantation locations of Leydig cells.

Why the use of alternative therapies for hypogonadism is not as popular as testosterone replacement therapy (TRT)?

- Limited research
- Lack of regulatory approval
- Low efficiency
- Physicians' preference

Conclusion

- Alternative therapies for hypogonadism exist, and they have shown promising results in some studies.
- However, their use is still being investigated, and regulatory bodies have not widely approved them.
- The effectiveness of alternative therapies may also vary depending on the severity of hypogonadism.
- It is, therefore, crucial to consult with a knowledgeable healthcare professional who can guide patients in selecting the most appropriate treatment option for specific condition and monitor his progress closely.


THANK YOU