

## Short Communication

# Bioidentical Hormone Replacement Therapy for Men in the Primary Care Setting

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### Introduction

In a prior article, I described the risks and benefits of optimized bioidentical hormone replacement therapy (BHRT) for aging men.<sup>1</sup> That article addressed the ambivalence of mainstream medical practitioners towards hormone replacement therapy (HRT), in general, and testosterone supplementation, in particular. Many primary care physicians (PCPs) lack special training in HRT and have been swayed by poorly designed clinical studies in which men treated with testosterone supplementation experienced a higher incidence of prostate cancer, myocardial infarctions, and other cardiovascular events. However, careful examination of the published clinical studies revealed that restoring testosterone to their optimal levels in aging male patients was unlikely to be the underlying cause of the reported adverse reactions. Instead, excessively high (uncontrolled) serum estradiol levels were identified as the most likely culprit for the adverse events.

### Resolving the Testosterone Controversy

Surprisingly, clinical trial investigators in more than a dozen published studies reporting adverse events from testosterone supplementation failed to control their male patients' excessive conversion of testosterone to estradiol catalyzed by aromatase. One such study even appeared in 2010 in the prestigious *New England Journal of Medicine* and was widely reported by the news media. In that study, medical doctor principal investigators dramatically boosted the testosterone levels without controlling for conversion to estradiol in elderly military veterans suffering from a variety of poor health conditions including obesity, diabetes, and chronic heart disease.<sup>2</sup> Left with uncontrolled aromatase conversions, these dilapidated men experienced sometimes fatal spikes in their serum estradiol levels.

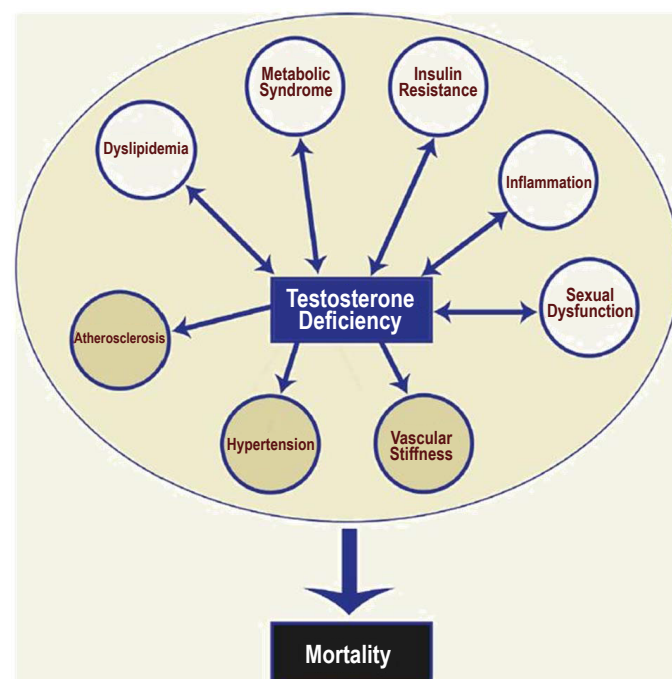
"In fact, elevated estrogen can sharply increase heart attack risk by promoting platelet aggregation and coagulation in coronary arteries.<sup>3,4</sup> Higher estrogen in men also increases inflammation which can cause unstable plaque to rupture and occlude a coronary artery, thus creating a sudden heart attack.<sup>5,6,7</sup> Abdominal fat tissue synthesizes large amounts of aromatase, which predisposed these elderly male clinical trial patients to harmful spikes in estradiol levels once testosterone was administered to them.

A majority of the published clinical studies of testosterone replacement therapy (TRT) in aging men have used synthetic testosterone drugs rather than natural, bioidentical testosterone, which is available in both topical lotions and gels as well as sublingual troches from compounding pharmacies. Aside from the striking difference in cost in which a 180-day supply of highly effective bioidentical testosterone troches can be purchased for just \$75, whereas Express Scripts as of October 2016 prices the synthetic testosterone pharmaceutical products

in the range of \$300-\$500/month, patients may prefer to take natural, bioidentical HRT over synthetic alternatives.<sup>8</sup>

In cohort studies, testosterone levels are associated weakly but consistently with muscle mass, strength, physical function, anemia, bone mass density and bone quality, visceral adiposity, and with the risk of diabetes mellitus, coronary artery disease, slip and fall incidents, fractures, and mortality.<sup>9</sup> The aging process is characterized by an imbalance between anabolic hormones that decrease (testosterone, dehydroepiandrosterone-sulphate (DHEA-S), estradiol, insulin like growth factor-1 (IGF-1) and Vitamin D) and catabolic hormones (cortisol) that increase.<sup>10</sup> Gradually reduced testosterone levels in aging males (secondary hypogonadism) result from dysfunction of the hypothalamic-pituitary-testes (HPT) axis and present clinically as fatigue, muscle weakness, loss of endurance, and erectile dysfunction. Aside from these visible signs of overall health, testosterone facilitates the reverse cholesterol transport from the linings of arteries to the liver for metabolism, thereby reducing the degree and incidence of atherosclerosis (Figure 1).

Absent some contraindication to TRT such as prostate or breast cancer, uncontrolled congestive heart failure, or erythrocytosis, PCPs should be offering BHRT options to their aging male patients.



**Figure 1:** Testosterone deficiency in men contributes to a host of co-morbidities. These include inflammation, insulin resistance, diabetes, dyslipidemia, hypertension, metabolic syndrome, vascular stiffness, atherosclerosis, cardiovascular disease, sexual dysfunction and mortality.<sup>13</sup>

## Starting Doses of Testosterone for Topical Application vs. Sublingual

The typical starting dose of testosterone for a man experiencing symptoms of andropause or natural declines in hormone levels with aging would be 100 mg q.d. (once per day) of bioidentical testosterone lotion or gel. The lotion or gel is typically applied each morning to alternating parts of the body, so that the skin in the application area does not become resistant to the testosterone over time. The lotions and gels are typically dispensed from a vial that requires four clicks or turns of the vial top. If the prescription for the topical testosterone lotion or gel is written instead for twice the patient's normal dose or 200 mg q.d., then the patient can obtain his 100 mg dose by two clicks of the vial, instead of the normal four clicks, and thereby use less lotion or gel each day. The practical effect will be to extend the vial from a 30-day supply to a 60-day supply typically for the same price. Most compounding pharmacies in the USA charge the same price for a monthly supply vial of testosterone gel or lotion for any dose up to 200 mg q.d.

However, I strongly recommend that PCPs prescribe to their male patients experiencing andropause symptoms the newer (sublingual) compounded testosterone troches, rather than testosterone lotions or gels. Sublingual absorption of testosterone is approximately ten times greater than through the skin. Thus the typical starting dose with testosterone troches will be just 10 mg q.d. To prevent overshooting of targeted levels for two-hour subsequent serum testosterone levels, the 10 mg dose is typically chopped in half with a 5 mg dose taken in the morning and a second 5 mg dose taken about 8 h later.

Patients who are familiar with chopping pills in half will have no trouble chopping a troche in half or even into quarters; the troches are soft and easier to chop than hard pills. If a testosterone troche prescription is written for 20 mg/troche instead of 10 mg/troche, then the patient desiring a 10 mg dose q.d. would consume two separate ¼ troche parts for 5 mg each b.i.d. (twice per day) eight to ten hours apart. Chopping a 20 mg troche into ¼ troche doses enables patients to receive their medication for a lower effective price. The only caveat is that the patient must verify with the compounding pharmacy when the troche efficacy will expire. For example, the patient may find that water-based flavors, e.g. chocolate and strawberry, will cause the troches to degrade and expire after 90 days; whereas using an oil-based flavor, e.g. spearmint or peppermint, may enable the troches to retain their efficacy for 180 days.

Male patients strongly prefer the convenience and efficacy of testosterone troches over topically applied gels and lotions. If a patient forgets a dose and is about to start some physical activity, for example working out at the fitness center, the testosterone troche can be placed sublingually, and the patient will have achieved his maximum absorption level within one minute. In contrast, the lotions and gels require two hours to achieve maximum absorption, thereby delaying the benefit to the patient from his workout and risking that his perspiration may expel the testosterone. To summarize this section, a reasonably intelligent patient who is comfortable with chopping pills and troches into quarters should commence BHRT with 20 mg testosterone troches chopped into ¼ troche doses of 5

mg each taken b.i.d. Other patients who are uncomfortable with chopping troches should begin BHRT with 5 mg testosterone troches taken b.i.d. approximately 8 h apart.

## Targeting Optimal Sex Hormone Levels in Men

Most PCPs are unaware that testosterone levels in men should fall within an optimal range to achieve therapeutic benefit. If a dozen PCPs were asked about the optimal free testosterone and total testosterone range for a 55 year old male, they would likely give us a dozen different answers. But optimal serum hormone levels have been identified in the medical literature, and PCPs need to apply these optimal ranges in their clinical practice. In reality, metabolism of the steroidal hormones creates a hormonal cascade of ever-changing levels of metabolites that must be optimized simultaneously (Figure 2).

For men, the three principal hormones requiring regulation are testosterone (both free and total), estradiol, and dihydrotestosterone (DHT). Each of those three hormones has a separate (generic) drug regulator, and thus TRT in reality is testosterone, estradiol, and DHT coordinated therapy. Life Extension Foundation, which has earned a well-deserved reputation as an institutional subject matter expert on HRT, defines the optimal range in men for free testosterone as 20-25 pg/mL, total testosterone 700-900 ng/dL, estradiol 20-30 pg/mL and DHT 30-50 ng/dL.

The Life Extension Male Hormone Protocol contains more than fifty references to the medical literature.<sup>11</sup> The interested reader is encouraged to investigate the scientific evidence justifying Life Extension's recommended optimal hormone levels. The Life Extension optimal ranges and the Labcorp reference ranges for these tests are shown in Table 1.

Patients who do not achieve their physical peak with total

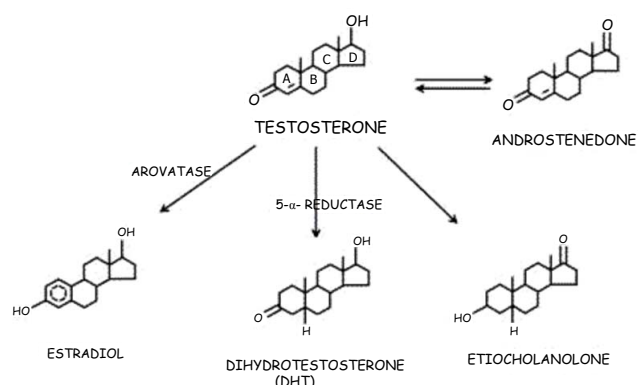


Figure 2: Biochemical pathways of testosterone metabolism.<sup>14</sup>

Table 1: Comparison of life extension optimal ranges and labcorp reference ranges.

Test	Life Extension optimal range	Labcorp reference range
Free Testosterone	20–25 pg/mL	7.2–24.0 pg/mL
Total Testosterone	700–900 ng/dL	(patient age 50-59) 348–1197 ng/dL
Estradiol	20–30 pg/mL	8–43 pg/mL
DHT	30-50 ng/dL	30-85 ng/dL

testosterone maintained in the 700–900 ng/dL intervals may feel better when they target higher total testosterone in the range of 1000–1200 ng/dL. Similarly, aging men at risk for osteoporosis may need to target estradiol in the 30–40 pg/mL in order to facilitate bone mineralization. Regardless of what targeted ranges are optimal for a given patient, the patient will need more frequent blood testing intervals than the typical annual or biannual standard. Patients will be surprised to find their hormones drift out of balance naturally even after they have stabilized on medicine dosing.<sup>12</sup>

When male patients begin BHRT, they will typically need a prescription for 0.5 mg of Anastrozole twice per week. Anastrozole is manufactured in 1 mg tablets, and thus the patient will chop the pill in half and take one-half tablet twice per week, e.g. on Mondays and Thursdays. To control DHT, the patient will need either Finasteride or Dutasteride, both of which are now available as generic drugs, although Finasteride is older and cheaper. PCPs should monitor patients taking Finasteride who initially maintain serum DHT targets but eventually experience rising DHT far exceeding the normal range. These patients will likely need to switch to Dutasteride, which inhibits Types I, II and III isoenzymes of 5  $\alpha$ -reductase, whereas Finasteride inhibits only Types II and III.

### Additional Considerations

When an external source of testosterone is absorbed by the male body, it typically causes partial atrophy of the HPT axis manifesting in testicular shrinkage. Endogenous production of testosterone and stimulation of the HPT axis can be obtained using a selective estrogen receptor modulator drug, such as Clomiphene. Male patients on BHRT who are attempting to procreate or who express concern with the testicular shrinkage side effect may benefit from 25 mg Clomiphene q.d. Additionally, some patients may wish to try dehydroepiandrosterone-sulfate (DHEA-S) supplementation prior to embarking on testosterone BHRT. The dose of DHEA-S will vary by patient, but a typical starting dose would be 25 mg q.d. for a patient experiencing symptoms of andropause.

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