In light of the potentially serious safety concerns associated with the use of testosterone supplementation alone in aging men, we respectfully suggest that the authors consider using androgen supplementation strategies that avoid the potential problems associated with the 5α-reduction of testosterone to DHT. A simple, safe, and effective treatment option in this regard may be to coadminister a 5α-reductase inhibitor as adjunctive therapy with a testosterone supplement. Such an approach would prevent the DHT elevation associated with testosterone supplementation, while still allowing for testosterone to exert its beneficial metabolic and anthropometric effects. We and others have extensively studied the use of 5α-reductase inhibitors in the treatment of aging men with benign prostatic hyperplasia (5); these drugs are well tolerated and have been shown to markedly suppress the reduction of testosterone to DHT.

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References

Relationship Between Testosterone Levels, Insulin Sensitivity, and Mitochondrial Function in Men

Response to Pitteloud et al.

We read with interest the excellent study by Pitteloud et al. (1) demonstrating that low serum total testosterone levels are associated with an adverse metabolic profile in aging men and suggesting a novel unifying mechanism for the previously independent observations that low testosterone levels and impaired mitochondrial function promote insulin resistance in these patients. The authors concluded their report by stating that there is a need for evaluation of the potential benefits of androgen supplementation in preventing or treating the metabolic syndrome and/or type 2 diabetes in men.

While we agree with their conclusion, we would like to provide the authors with a cautionary comment regarding the means by which androgen levels should be supplemented in these patients. The most commonly used method to increase androgen levels in aging, hypogonadal men is to administer testosterone supplementation therapy (2). From a urological perspective, a major problem with the use of testosterone supplementation alone in aging men is that the exogenously administered testosterone is metabolized by 5α-reductase to dihydrotestosterone (DHT). Based on newly emerging data from the National Cancer Institute–sponsored Prostate Cancer Prevention Trial, DHT is a proven risk factor for the development of prostate cancer in aging men (3). Moreover, the use of testosterone supplementation alone in men with low serum testosterone levels has been shown to lead to an elevation in their intraprostatic DHT levels (4).

In light of the potentially serious safety concerns associated with the use of testosterone supplementation alone in aging men, we respectfully suggest that the authors consider using androgen supplementation strategies that avoid the potential problems associated with the 5α-reduction of testosterone to DHT. A simple, safe, and effective treatment option in this regard may be to coadminister a 5α-reductase inhibitor as adjunctive therapy with a testosterone supplement. Such an approach would prevent the DHT elevation associated with testosterone supplementation, while still allowing for testosterone to exert its beneficial metabolic and anthropometric effects. We and others have extensively studied the use of 5α-reductase inhibitors in the treatment of aging men with benign prostatic hyperplasia (5); these drugs are well tolerated and have been shown to markedly suppress the reduction of testosterone to DHT.

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Relationship Between Testosterone Levels, Insulin Sensitivity, and Mitochondrial Function in Men

Response to Kaplan and Crawford

I thank Drs. Kaplan and Crawford (1) for their kind remarks on our article (2) on the relationship between testosterone levels and insulin sensitivity in men and for their thoughtful comments on the optimal form of androgen replacement for older men.

While the standard form of androgen replacement for hypogonadal men is testosterone, the authors express concern about its use in older men, given that it results in an increase in levels of dihydrotestosterone (DHT), which, in as-yet unpublished data, has been identified as a risk factor for prostate cancer (3). On this basis, Drs. Kaplan and Crawford recommend that a regimen comprising coadministration of testosterone with the 5α-reductase inhibitor finasteride be considered for androgen replacement in older men.

Preliminary evidence suggests that this may indeed be a reasonable strategy. In a carefully conducted three-arm study (testosterone alone, testosterone plus 5 mg/day finasteride, and placebo) of 70 men aged ≥65 years with testosterone levels <350 ng/dl, Tenover and colleagues (4,5) demonstrated that testosterone therapy both alone and in combination with finasteride improved body composition, physical performance, bone mineral density, and total cholesterol. However, concomitant treatment with finasteride ap-