Taking the first steps in establishing recommendations for testosterone monitoring in men with prostate cancer on androgen-deprivation therapy

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The paper by Shayegan et al in this issue of *CUAJ* represents an important initial step in establishing recommendations for hormonal monitoring in men with prostate cancer on androgen-deprivation therapy (ADT).

As with most subjects related to the actions of testosterone, the survey adds to the controversies, but also opens the opportunity to explore several of the concerns relevant to the hormonal management of prostate cancer.

Possible reasons for survey findings

The inconsistencies in monitoring serum testosterone among specialists are not surprising and are related to several factors that militate against unanimity of criteria, such as:

1. The lack of consensus on the definition of "castrate" levels of testosterone (1.7 vs. 0.7 nmol/L). Although the preponderance of the evidence indicates better outcomes for the lower values, over a quarter of the specialists don't believe it is worth monitoring.
2. As indicated in the paper, breakthrough rates are relatively low for patients on luteinizing hormone-releasing hormone (LHRH) agonist therapy, and probably lower for those on LHRH antagonists[1] and after orchiectomy. Thus, some may simply prefer to use surrogate measures, such as prostate-specific antigen (PSA), before testing for testosterone levels.
3. Although there is universal familiarity with the testosterone flare (and its prevention) in the first week of LHRH agonists administration, less is known about the significance of additional surges in testosterone occurring either upon re-injection or at any time during treatment with these agents (references 2 and 4 in the Shayegan paper). Therefore, it seems incongruous that most responders monitoring testosterone would do so before each treatment (40.5%) or once a year (35.3%), since the probability of not detecting these surges is quite substantial.
4. Uncertainty about the significance of serum testosterone determinations stem from the finding that they are a poor reflection of prostate tissue androgen levels,[2] but perhaps more confounding is the realization that following medical castration, there is a decrease of 94% in serum testosterone levels while intraprostatic testosterone and dihydrotestosterone remain at 20–30% of pre-castration levels.[3]
5. There is much controversy about testosterone administration to men with prostate cancer[4] and a tendency to believe that it is safe, so why the need to aim at and document "castrate" levels in these men?
6. The perceived unreliability of standard laboratory testing is the result of problems in the biochemical assessment of hypogonadism and has been unjustifiably transferred to the management of prostate cancer.

Opportunities opened by the survey

1. The term "castrate level" is misleading since only a small minority of patients undergo orchiectomy. For this reason, the terms "optimal" (≤0.7 nmol/L) vs "suboptimal" have been proposed for patients on ADT.[5] In addition, the American and European literature generally report testosterone values in different units (ng/dl). This adds confusion for clinicians. Suffice to remember that 0.7 nmol/ is 20 ng/dl or that ngl/dl x 0.03467 converts the value into nmol/L. (Note: There are conversion apps available on the web).
2. The putative detrimental effect of suboptimal testosterone concentrations that occur during ADT calls for increasing awareness of the problem by specialists. The most consistent suppression of testosterone is achieved with surgical castration and LHRH antagonists. About 80% of surgically castrated men achieved levels <1.7 ng/dl while only 65% do so on goserelin (reference 2 in the Shayegan paper).
3. The survey pointed to the significant inconsistencies among practitioners on testosterone monitoring during treatment. Although it is convenient to assess testoster-

one levels coincidentally with treatment (as 40.5% of responders do), it is also dissonant with what is known about breakthroughs and surges during ADT. Guidelines are needed to define the frequency and timing for measuring testosterone.

4. Men with prostate cancer failing ADT clearly deserve re-assessment of the efficacy of such treatment to rule out a possible relationship with suboptimal androgen suppression.
5. Expert recommendations are also required to explain the options for management of cases where the nadir of ≤0.7 nmol/L for serum testosterone is not achieved on continuous ADT.
6. An alluring research opportunity would be to investigate whether the documented disagreement between serum and intraprostatic androgen concentrations found in healthy men[3,6] also exists in metastatic castration-resistant tissue compared to primary prostate cancer.[7]
7. Concerns about the unreliability of laboratory testing for serum testosterone stems from problems arising in assessing hypogonadism. Intraindividual biological variations[8] are inconsequential in men on ADT, while interindividual ones may carry prognostic significance.[9] Analytical variations remain relevant in this cohort. The importance of effective communication and understanding the needs of the clinician and the capabilities of the laboratory cannot be overemphasized. The survey clearly indicates that we are floundering in this area: 79% of the responders do not know the methodology used by the local laboratory.

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