



Review Article

Reporting and ideal testosterone levels in men undergoing androgen deprivation for prostate cancer—time for a rethink?



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ABSTRACT

Background: This study aims to review current laboratory reporting strategies across Australia and New Zealand with a view to propose a more useful template for reporting serum testosterone in the context of prostate cancer.

Materials and methods: Registered pathology laboratories in Australia and New Zealand were enrolled into the current study. An electronic or a phone survey was utilized to collect data from each participating laboratory. Obtained information included assay utilized, units reported, reference intervals, lowest reported value, and lowest detectable value. To identify recommendations for testosterone testing, a systematic search was performed across Web of Science (including MEDLINE), EMBASE, and Cochrane libraries.

Results: Assessment of national pathology laboratories identified significant heterogeneity in the reporting methods. Reports typically used a “normal healthy male of 35 years of age” as a comparator but did not refer to optimal castrate levels, the lowest level that their assay was able to detect, nor did they include appended clinical guidelines relating to the prostate cancer patient cohort.

Conclusions: Across Australia and New Zealand, various methods for testing and reporting serum testosterone exist, while international guidelines remain vague. The fashion in which serum testosterone levels are displayed should be re-evaluated to address the relevant clinical population and reflect an agreed-upon castrate threshold in patients undergoing androgen deprivation therapy.

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1. Introduction

Since the 1940s, serum testosterone (T) has marked the cornerstone of prostate cancer (PC) progression as postulated by Huggins and Hodges,¹ suggesting a direct correlation between high levels of T and PC progression. This highlights the rationale for castration, traditionally surgical, in an attempt to lower serum T and limit PC progression. Over the last 3 decades, androgen deprivation therapy (ADT) has been introduced as an alternative to surgical castration to achieve castration in the treatment of advanced PC.² Historically, the recommended castrate threshold was below 1.7 nmol/L (50 ng/dL), and this value is still referenced by some regulatory authorities and utilized in clinical trials.³

However, recent studies have conferred better oncological outcomes, with an even lower T threshold of 0.7 nmol/L (20 ng/dL).^{3–5} This has resulted in changes to international guidelines including a recent statement from the European Association of Urology promoting this lower threshold.³

Despite the identification of the importance of ensuring castrate levels of T during ADT, the manner in which serum T is reported has not been re-evaluated in recent times. The absolute values assist in clinical decision making, underpinning the importance of their accuracy. However, at present, T levels are still reported in the context of men being assessed for hypogonadism rather than therapeutic castration. Typical threshold levels for hypogonadism are generally >12 nmol/L (346 ng/dL),⁶ values that hold little significance in the setting of ADT (see Fig. 1). Similarities may be drawn in the assessment of biochemical recurrence after definitive treatment for PC—where accurate prostate-specific antigen (PSA) levels at the lowest detection points are critical and may affect management.

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PSA-prostate-specific antigen								
Req no:	P479691	P033778	P065878	P197767	P488829			
Date:	08/11/14	24/01/15	14/02/15	09/05/15	07/11/15			
Time:	08 : 40	09 : 06	08 : 33	08 : 55	08 : 55	Units	Ref	Range

Reproductive hormones (serum/plasma)								
Testost	<0.4 L			<0.4 L	<0.4 L	nmol/L	12.0–31.9	
Tumor markers (serum/plasma)								
PSA	<0.03		<0.03	<0.03	<0.03	µg/L	<6.5	
Bone markers (serum/plasma)								
CTX	1,094					µg/L	See–below	
P1NP	62					µg/L	See–below	

Total testosterone male reference interval derived from morning samples from healthy young (<35 y.o.) men.

Lower levels are seen with increasing age, coexisting illness, obesity and insulin resistance and require interpretation within the clinical context

CTX-telopeptide reference ranges:

Female	(20–49 years)	150–800
	(50–70 years)	50–800
	(>70 years)	100–1000
Male	(20–24 years)	400–900
	(25–70 years)	100–600
	(>70 years)	100–750

Harmonized Australian reference intervals in use from 11/03/2015

P1NP reference ranges:

Female	(20–24 years)	15–90
	(25–49 years)	15–70
	(50–70 years)	15–90
	(>70 years)	15–115
Male	(20–24 years)	15–115
	(25–70 years)	15–80
	(>70 years)	15–115

Harmonized Australian reference intervals in use from 11/03/2015

Austin Pathology, Austin health (APA). NATA/RCPA lab accred'n no 2741
A/prof T Leong, Dr Marcel Leroi, DR Q Lam, A/prof C Smith

Fig. 1. Typical testosterone pathology report. CTX, C-terminal telopeptide; P1NP, Procollagen-1 N-terminal propeptide; PSA, prostate-specific antigen; Testost, testosterone; y.o., years old.

In the setting of ADT, clinicians are truly interested in information that pertains to the following:

- (1) How low the T level is (as an absolute value in preference to an interval where possible).
- (2) The lowest T level the laboratory is able to detect.
- (3) Accurate clinical guidance as to what the level indicates often in the form of a clinical note.

Variations as to what levels are considered “ideal” exist among international guidelines. This has prompted the need for advisory offering recommendations on the optimal levels and timing of tests. In this study, we aimed to determine the current standards of T reporting from pathology laboratories across Australia. Further, we aimed to review the current guidelines in T monitoring in the setting of ADT.

2. Materials and methods

2.1. Survey of pathology laboratories

A list of registered pathology laboratories in Australia and New Zealand was obtained from business listings and the register at the

Royal College of Pathologists of Australasia. Laboratories were contacted and enrolled into the current study, and laboratory reporting data were collected via a phone survey. Questions were directed to a senior laboratory staff member, and in the case that the member of staff was unable to give a verbal response, the questions were sent to them via e-mail. The corresponding answers were entered into the survey template and returned by e-mail. Data collected from each participating laboratory included the following: laboratory information (region/city) and T testing information (manufacturer and analyzer utilized, T assay utilized, T units reported, T reference intervals, lowest reported T value, and lowest detectable T value). In addition to this laboratory-specific data, the awareness of T-lowering medication and reporting standards in this population were assessed.

2.2. Construction of a clinical reporting guideline to be issued with reports of serum T

We performed a systematic search to identify all locoregional reporting guidelines for T. Specifically, we aimed to identify articles that outlined the reporting strategies and recommended frequency of T in patients on ADT. To obtain relevant articles, we

Table 1
Data obtained from surveys of major pathology laboratories in Australia.

Pathology laboratory	Assay used	Units reported	Interval	Limit of blank (lowest reported value; nmol/L)	Limit of quantification (lowest detectable value)
Melbourne Dorevitch	Siemens Centaur immunoassay (Siemens, Berlin, Germany)	nmol/L	8.3–30.2	<0.3	LoD
Melbourne Pathology	Electrochemiluminescence immunoassay	nmol/L	9.9–28.8 (over 35 yr)	<0.4	<0.4 nmol/L
St Vincents	Architect system chemiluminescent microparticle immunoassay (Abbott Laboratories, IL, USA)	nmol/L	8.0–30.0	<0.2	<0.1 nmol/L
Healthscope Sydney	Siemens Centaur immunoassay (Siemens, Berlin, Germany)	nmol/L	8.0–30.0	<0.4	LoD
South Eastern Area Laboratory Services	Siemens Immunolyte 2000 (Siemens, Berlin, Germany)	nmol/L	5.6–23.6	<0.7	LoD
Douglas Hanly Moir	Abbott Architect (Abbott Laboratories, IL, USA)	nmol/L	9.5–28 (over 36 yr)	<0.1	LoD
San Path St Vincents Hospital	Roche Cobas 601 (Roche, Basel, Switzerland) (electrochemiluminescence immunoassay)	nmol/L	9.9–27.8	0.087–52.000	<0.069 nmol/L
Laverty New Zealand	Siemens Centaur immunoassay (Siemens, Berlin, Germany)	nmol/L	8.3–28.7	<0.4	LoD
Pathlab	Beckman Coulter DXI (Beckman Coulter, Brea, CA, USA)	nmol/L	9.0–30.0	<0.35	LoD
Southern Community Laboratories (Healthscope)	Roche chemiluminescent assay (Roche, Basel, Switzerland)	nmol/L	8.0–38.0	<0.40	0.09 nmol/L
Medlab Central (Douglas Hanly Moir)	Roche chemiluminescent assay (Roche, Basel, Switzerland)	nmol/L	Tiered to patient	<0.4	0.416 nmol/L
Northland Pathology (Healthscope)	Roche Cobas 601 (Roche, Basel, Switzerland) (electrochemiluminescence immunoassay)	nmol/L	8.0–29.0	<0.5	0.087 nmol/L

LoD, limit of detection.

systematically searched Web of Science (including MEDLINE), EMBASE, and Cochrane. The following search terms were used: “prostate cancer” (/exp, prostat* ca*, prostat* neo*), “testosterone” (/exp, testoster*), “androgen deprivation” (/exp, andro*, depriv*, castrat*), +/- “survival” (/exp, surviv*). In addition, we systematically searched national and international urological, oncological, and pathology bodies’ databases and documentation for respective

PC guidelines. These guidelines were reviewed for recommendations on T testing and T reporting by pathology laboratories.

2.3. Statistical analysis

Survey data were collated into an Excel 2007 spreadsheet (Microsoft Excel, Redmond, CA, USA). Minimal statistical analysis

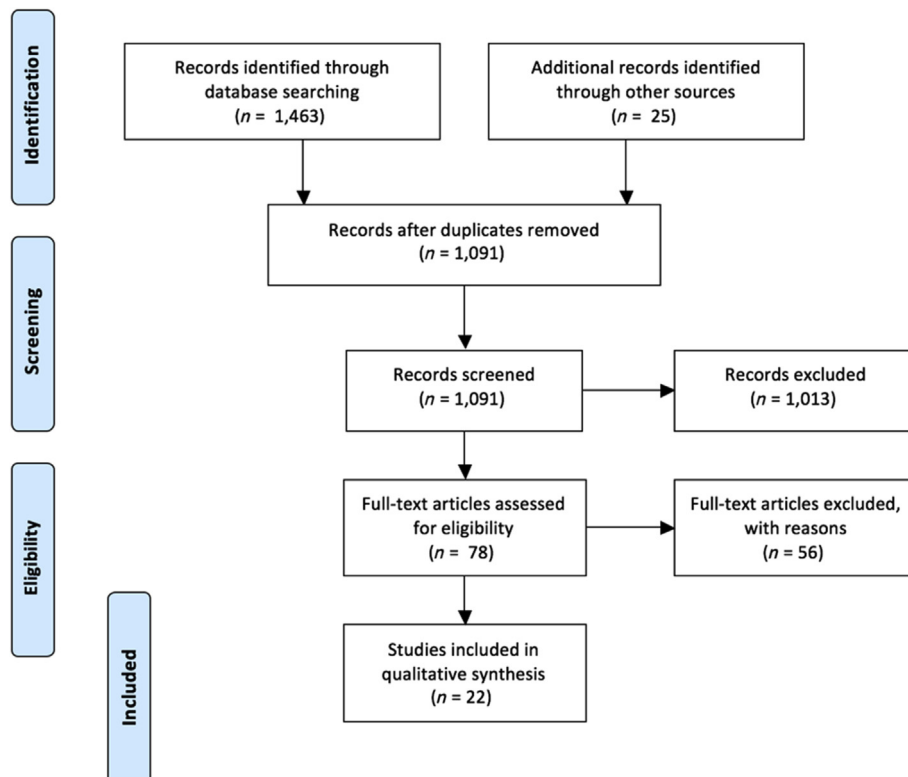


Fig. 2. Summary of systematic search.

was performed. Available data were reported as frequencies unless otherwise specified.

3. Results

3.1. Reporting

The data from the survey of pathology laboratories are outlined in Table 1. On assessment of reporting standards, all laboratories reported T intervals and clinical guidelines in a similar fashion with the focus on “normal” T levels. A typical example of how T levels are currently reported is included in Fig. 1. No laboratory reported castrate levels of T or the lowest level that the respective assay was able to achieve. Further, within these pathology T reports, no clinical guidelines were appended to guide clinicians treating men with PC.

3.2. Current guidelines and recommendations for reporting T in men on ADT

From our systematic search strategy, we identified 78 articles relevant for assessment (Fig. 2). Of these articles, we identified eight recommendations regarding T testing in patients on ADT. Pertinent guidelines were identified from the National Comprehensive Cancer Network,⁷ the European Association of Urology,⁸ the Canadian Urological Association,⁹ and the American Urological Association.¹⁰ Their respective recommendations are summarized in Table 2.

3.3. Construction of a clinical reporting guideline to be issued with reports of serum T

After examining current reporting by international guidelines, a proposed T reporting schemata may include the following (example template is highlighted in Fig. 3):

- (1) Absolute level of T in the designated units.
- (2) Reference intervals for the normal male.
- (3) Lowest interval and highest values obtained by the respective assay (e.g., <0.4–100 nmol/L).
- (4) Pertinent clinical guidelines at the bottom of the report to state that “international guidelines recommend a serum testosterone level to be at least <0.7 nmol/L⁷ or <1 nmol/L in the setting of androgen deprivation for prostate cancer”.⁸
- (5) Recommendations for repeat testing in the setting of ADT for PC: it would be reasonable to test serum T at least 6 monthly or when a rise in serum PSA and/or clinical progression occurs while on ADT.

4. Discussion

A significant proportion of PC patients present with advanced disease.¹¹ In these patients, assessment of T levels during the early stages of ADT is critical in ensuring appropriate treatment of PC. Furthermore, during ADT treatment, T monitoring may assist in ensuring acceptable castration or the diagnosis of castrate-resistant PC. Despite increasing evidence, the optimal role and frequency of monitoring of T are not clear. The pertinent findings of the current study are multiple. First, we outlined the heterogeneity and loss of pertinent data when T values are reported by pathology laboratories. Further, we identified the significant variation in recommendations for T monitoring from the major urological and oncological authoritative bodies.

While T does not directly cause prostate dysplasia, it is considered imperative for the growth and progression of PC.^{12,13}

Table 2
Summary of clinical guidelines for testosterone testing.

Guidelines	Castrate serum T level	Frequency of testing serum T	If castrate level are not met
National Comprehensive Cancer Network, USA	1.7 nmol/L (50 ng/dL)	No frequency outlined but testing is mandatory in the face of rising PSA or clinical progression during ADT.	Further hormonal manipulation.
European Association of Urology	0.7 nmol/L (20 ng/dL)	3–6 monthly Must be evaluated in patients with rising PSA and/or clinical signs of progression to confirm a castrate-resistant state	Switch to another LHRH agonist or antagonist or to surgical orchiectomy should be considered
Canadian Urological Association	1.7 nmol/L (50 ng/dL)	None	None
American Urological Association	1.7 nmol/L (50 ng/dL)	None	None

ADT, androgen deprivation therapy; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.

	Date XX/XX/XX	Reference range	
Testosterone level	XX.XX nmol/L	12.0–31.9 nmol/L in healthy males ^(a)	Assay type: XXX
		<0.7 nmol/L in males undergoing ADT for PCA ^(b)	Testing intervals from assay: (<0.4–100 nmol/L)

Fig. 3. Sample template for serum testosterone reporting. ^{a)} Total testosterone male reference level derived from morning levels from young healthy men (<35 years old). NB: Lower levels are seen with increasing age, concurrent illness, obesity, and insulin resistance, and thus require interpretation in clinical context. ^{b)} For prostate cancer patients on ADT: recommendations in accordance with the European Association of Urology guidelines.³ It may be clinically indicated to repeat serum testosterone levels at least 6 monthly or when a rise in serum prostate-specific antigen and/or clinical progression occurs while on ADT. ADT, androgen deprivation therapy; PCA, prostate cancer.

Physiologically, T has three endogenous sources in the male, predominantly from the Leydig cells in the testis and small amounts from the zona reticularis in the adrenal glands and specific PC cells. Only 1–2% of T circulates in the blood freely, constituting the active form of the hormone, which is able to bind to androgen receptors. The remaining T is bound to plasma proteins, predominantly to sex hormone binding globulin and weakly to albumin, in a reversible manner, becoming biologically active in certain tissues.¹⁴ Hormonal therapies influence the binding of T to sex hormone binding globulin, thereby altering the biologically active fraction of T. As a consequence, laboratories correct for sex hormone binding globulin when reporting free T.¹⁵ T samples are best taken in the morning when circulating T levels are highest, with most laboratories using the method of automated chemiluminescent immunoassays or similar principles.¹⁶

The findings of the current study highlight the limitations of the current format of pathology reporting of serum T in the context of PC patients, which thus requires re-evaluation. Our study illustrates that in Australia, low serum T levels are typically reported as below threshold values that are significant for a diagnosis of hypogonadism (e.g., <12.0 nmol/L), rather than as an absolute measure. In the setting of PC, castration was typically achieved by means of bilateral orchiectomy. Recent advances in pharmacotherapy have led to the introduction of gonadotrophin-releasing hormone or luteinizing hormone-releasing hormone to achieve chemical castration. Despite increased morbidity,^{17,18} chemical castration remains the mainstay of treatment. Absolute values of T allow the clinician to ensure acceptable levels of castration during ADT. Patients who do not achieve a minimum T level of <0.7 nmol/L in their 1st year of ADT have been reported to have a significantly higher risk (HR) of developing castrate-resistant PC [0.7–1.7 nmol/L: Hazard Ratio (HR), 1.62; 95% confidence interval (CI), 1.20–2.18; ≥1.7 nmol/L: HR, 1.90; 95% CI, 0.778–4.70].⁵ Additionally, in the case of men who do not reach “ultra” low serum T, earlier castration resistance ensues due to the higher number of partially resistant cells persisting.¹⁹ Accordingly, reporting regimes that neither provide objective values nor the lowest detectable value for the assay are insufficient. Re-evaluation of the current reporting schemata should take into account the important roles that T plays, and the necessity for prompt and accurate interpretation.

Our review identified a stark absence of objective guidelines outlining the optimal use of T testing in the setting of ADT. A consensus on the following parameters is required: definition of castrate levels of T, frequency at which T should be performed during ADT, and what to do when targets are not met. Historically, the most common definition for castrate quoted in the literature is a measured level of T of 1.7 nmol/L (50 ng/dL), derived from studies in the late 1960s and early 1970s.²⁰ Alternatively, several authors consider 0.7 nmol/L (20 ng/dL) T as the lower limit, as this is the value obtained with orchiectomy.²¹ These lower T values are

supported by the growing body of evidence suggesting that lower T during ADT infers superior oncological outcomes.^{5,22,23} Advocates of the continued use of 1.7 nmol/L (50 ng/dL) T as the lower limit argue that there is no difference in the follow-up of patients regarding the decrease in PSA and the evolution of PC with either 0.7 nmol/L or 1.7 nmol/L (20 ng/dL or 50 ng/dL) T.²⁴ Regarding the frequency of T monitoring, a recommendation from a recent study suggests that patients initiating ADT should have their T and PSA levels monitored regularly during the 1st year of treatment. T should be assayed just before the next androgen-lowering injection to ensure a sustained response through the dosing interval. Not achieving a T level of 0.7 nmol/L (20 ng/dL) during the 1st year of ADT should prompt consideration of a change in hormone therapy or to bilateral orchiectomy (if continuous therapy is intended).⁵

The limitations of this study include those inherent to survey-based data. In current literature, there are considerable interest and scope for research on the role of T in advanced PC. No doubt, further large robust prospective study assessing the role of T in oncological outcomes will improve knowledge on PC progression and improve treatment. With this information, the role of monitoring T during ADT will become clearer.²⁵

A growing body of evidence highlights the role of maximal T suppression in men on ADT for PC. In Australia, there is no agreed standard for the monitoring of serum T in patients undergoing ADT. Nor is there a standard template for the reporting of T in this patient cohort, which may lead to confusion for both the patient and the clinician. The fashion in which these results are displayed must be re-evaluated as per the proposed schemata to assist in interpretation by clinicians and enhancing patients' understanding. Alongside this, a joint position statement between authoritative bodies should be agreed upon to facilitate clinicians in optimization of T monitoring in patients on ADT.

Conflicts of interest

All authors have no conflict of interest to declare.

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