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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 achieve, 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.

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 specifi

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 testosterome 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 interpretaion 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. PSA, prostate-specific antigen; Testost, testosterone; y.o., years old. Q13

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 systematically searched Web of Science (including MEDLINE), EMBASE, and Cochrane. The following search terms were used: "prostate cancer"

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