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EDITORIAL OPEN ACCESS

Should laboratory assay quality be described in study publications and clinical guidelines? A focus on testosterone assay performance

Sudarshan Ramachandran, Mark Livingston, Geoffrey Hackett, Richard C. Strange

Over the past 25 years evidence based medicine has been increasingly used by healthcare professionals in the United Kingdom in the development of guidelines. According to Sackett et al in 1996, a "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" integrates clinical expertise with evidence from systematic research [1]. More recently Djulbegovic and Guyatt in 2017 suggested that evidence based medicine has ensured clinical medicine adopted trustworthy guidelines based on science and evolving methodology [2]. It is our view that the clinical laboratory has a major role in ensuring that recommendations based on biochemical measurements are robust.

To illustrate this point we highlight laboratory issues that support the British Society for Sexual Medicine (BSSM) guidelines on adult onset testosterone deficiency [3]. The guidelines state that men with total testosterone <8 nmol/l (230.74 ng/dl) or free testosterone <0.180 nmol/l (5.19 ng/dl) usually require testosterone therapy (TTh) while men with total testosterone levels between 8–12 nmol/l (230.74–346.10 ng/dl) may require TTh depending on the presence of symptoms associated with testosterone deficiency.

The studies included in the BSSM guidelines using testosterone levels used to characterise or determine the study cohort to identify men who may benefit from TTh are shown in Table 1 [4–12]. Importantly, only two of the nine studies in Table 1 described the specific assays used and none provided information on assay performance [7, 8]. As the BSSM and other guidelines have used specific testosterone concentrations to identify men who should be considered for TTh, standardisation of the assays used to measure concentrations of this analyte together with data on assay accuracy and precision are essential. Further, since two of the studies stratified the cohorts using reference ranges [4, 9] it is also important that universally accepted reference ranges are used in comparisons of patient cohorts. Such ranges may of course vary between populations.

It is hoped that the programs such as that of the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/labstandards/pdf/hs/HoSt_Brochure.pdf - accessed 04/04/2019) and the availability of reference materials will help assay manufacturers and laboratories to standardise testosterone methods. This is essential if action thresholds are suggested by guidelines and protocols. Interestingly, Cao et al in 2017 distributed four samples (2 males and 2 females) to 142 accredited laboratories (testosterone concentrations: 15.5 ng/dl (0.54 nmol/l), 30 ng/dl (1.04 nmol/l), 402 ng/dl (13.94 nmol/l) and 498ng/dl (17.27 nmol/l) and studied assay performance compared to target values using reference measurement procedures operated by the CDC reference laboratory [13]. It was observed that considerable bias existed for all the distributed samples –17.8% to 73.1%, 3.1% to 21.3%, –24.8% to 8.6%, and –22.1% to 6.8% for the four samples respectively. Similarly wide variation of assay performance are reported by Birmingham Quality on behalf of the National External Quality Assessment

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Table 1: Studies included in the BSSM guidelines using testosterone levels used to identify men who may benefit from testosterone therapy

Study	Testosterone assay	Number of Centres	Reporting of assay performance (Y/N)
Anderson et al. [4]	immunoassay, multiple methods	multiple	N (stratification based on laboratory reference ranges)
Basaria et al. [5]	not specified	single	N
Cheetham et al. [6]	not specified	multiple	N
Hackett et al. [7]	Roche Immunoassay	single	N
Muraleedaran et al. [8]	Bayer Advia Centaur & DRG immunoassay	two	N
Sharma et al. [9]	multiple methods, not specified	multiple	N (stratification based on laboratory reference ranges)
Shores et al. [10]	immunoassay	multiple	N
Traish et al. [11]	not specified	single	N
Vigen et al. [12]	not specified	single	N

BSSM: British Society for Sexual Medicine

Service (NEQAS) on steroid hormones (https://birminghamquality.org.uk/assets/doc/eqa/ster-453.pdf - accessed 03/04/2019) having distributed samples to over 200 laboratories in June 2018. The following method specific mean values were seen for male testosterone.

Sample A: All methods trimmed mean = 26.8 nmol/l (772.3 ng/dl), Abbott Architect = 29.9 nmol/l (861.7 ng/dl), Beckman Access = 21.7 nmol/l (625.4 ng/dl), Roche Cobas / Modular = 27.7 nmol/l (798.3 ng/dl), Siemens ADVIA Centaur = 25.0 nmol/l (720.5 ng/dl), Siemens Immulite 2000/25000 = 23.0 nmol/l (662.8 ng/dl) and Tandem Mass Spectrometry = 26.1 nmol/l (752.2 ng/dl).

Sample B: All methods trimmed mean = 19.8 nmol/l (570.6 ng/dl), Abbott Architect = 21.5 nmol/l (619.6 ng/dl), Beckman Access = 17.3 nmol/l (498.6 ng/dl), Roche Cobas / Modular = 19.8 nmol/l (570.6 ng/dl), Siemens ADVIA Centaur = 18.1 nmol/l (521.6 ng/dl), Siemens Immulite 2000/25000 = 36.8 nmol/l (1060.5 ng/dl) and Tandem Mass Spectrometry = 19.5 nmol/l (562.0 ng/dl).

Sample C: All methods trimmed mean = 18.9 nmol/l (544.7 ng/dl), Abbott Architect = 20.9 nmol/l (602.3 ng/dl), Beckman Access = 15.6 nmol/l (449.6 ng/dl), Roche Cobas / Modular = 19.2 nmol/l (553.3 ng/dl), Siemens ADVIA Centaur = 18.2 nmol/l (524.5 ng/dl), Siemens Immulite 2000 / 25000 = 14.7 nmol/l (423.6 ng/dl) and Tandem Mass Spectrometry = 18.7 nmol/l (538.9 ng/dl).

From this NEQAS report, only the medians / interquartile ranges for the Accuracy (A) score for the mass spectrometry and Roche Cobas assays appear to be within target. For the results given for the Beckman Access / Dxi, the bias on one specimen reported was -40.8% (from the target), and between-laboratory agreement for the same method gave coefficients of variation at levels under 10 nmol/L (288.2 ng/dl) of >25%.

It is clear that considerable variation exists in testosterone assay performance and that publications often contain little information of assay performance which is essential in the interpretation of data from studies. Hence, we recommend the following measures to provide better healthcare with greater consistency:

- Assay performance of local laboratory methods is made available to clinicians and bodies drawing up guidelines and protocols.
- Data from quality assurance distribution are made available to bodies drawing up guidelines and protocols.
- Laboratory personal and representatives from quality assurance schemes play a part in guideline forming committees.
- Harmonisation of laboratory function regarding reference ranges and advice provided to clinicians is audited. It must be ensured that pre-analytical requirements and the advice provided by the laboratory are based on current evidence.
- Greater detail of types of assays and performance is included in publications.
- Pressure should be applied to all manufacturers to use international reference preparations (e.g. CDC) to better standardise the measurement of testosterone concentration to reduce analytical variation, analogous to the International Federation of Clinical Chemistry's standardisation of haemoglobin A1c.

Keywords: Adult onset testosterone deficiency, Clinical guidelines, Laboratory performance, Testosterone therapy, Testosterone assays

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Author Contributions

Sudarshan Ramachandran – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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