Measurement and reporting of clinical testosterone diagnostics: a European survey

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BEED
Better estimates of hormonal exposure to improve diagnosis and treatment in endocrine diseases

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1. Study Synopsis

Title of study	Measurement and reporting of clinical testosterone diagnostics: a European survey.
Sponsor name	KU Leuven, Belgium
Principal Investigator	Prof. Dr. Leen Antonio
Medical methodology under investigation	Steroid diagnostics in clinical laboratories
Study purpose	Mapping practice on steroid hormone diagnostics in clinical laboratories throughout Europe.
Study Design	Non-interventional, monocentric prospective online survey study.
Endpoints	Methodologic information on measurements of: - Testosterone - Sex hormone-binding globulin (SHBG) - Free testosterone - Bioavailable testosterone
Summary of eligibility criteria	Clinical laboratories (hospital-affiliated or private sector) located in Europe.

2. Background and rationale

Steroid hormones, such as sex steroids (androgens and estrogens), glucocorticoids and vitamin D, are of vital physiological importance from fetal life to adulthood. Three fractions circulate in plasma: the unbound (free) fraction, the fraction bound to specific binding proteins, such as sex hormone-binding globulin (SHBG) and vitamin D binding protein (DBP); and the albumin-bound fraction. The equilibrium state between these fractions is characterized not only by total hormone concentration, but also by BP concentration and binding affinities for their respective metabolites[1].

Routinely used analytical techniques in clinical laboratories mostly only measure total hormone levels and further rely on calculators to estimate free hormone concentrations, taking into account BP characteristics (concentration and binding affinity)[2]. The use of calculators, relying on historically determined BP affinity constants in healthy populations, could however lead to inaccurate assessment of the free fraction, especially in patients in whom BP characteristics are altered, e.g. chronic kidney disease (CKD), pregnancy, liver disease and obesity[2].

In conditions where BP characteristics are altered, a direct measurement of free hormone levels could lead to a more correct diagnosis and therapeutic intervention. Direct measurement is however laborious, requires specialized equipment and staff expertise and is only done in a limited number of centers[3].

Measuring total testosterone in serum is paramount in the diagnostic work-up of male hypogonadism. However, adding free testosterone to the diagnostic panel of male hypogonadism could increase diagnostic sensitivity. Professional societies, such as the European Academy of Andrology and the Endocrine Society, decided to amend its guidelines on the diagnosis of hypogonadism in men, including free testosterone as an additional parameter[4,5].

However, a precise definition of the lower limit of 'normal' total testosterone still remains ambiguous. For hypogonadism, guidelines recommend using local populations to validate total testosterone assays in order to create population-based reference ranges [3]. Lacking a golden standard calibrating specimen, this results in various reference ranges being used in different clinical laboratories around the world. For free testosterone on the other hand, technical difficulties delay implementation in clinical routine. Between clinical laboratories, free testosterone is sometimes measured, but more often calculated. This results in an even greater variance of test characteristics (e.g. used formula) and reference ranges.

3. Study objectives and Design

3.1 Study objectives

This survey will serve as a tool to map current clinical diagnostic practices concerning (free) steroid hormone measurements/calculations. To date, analogous surveys have only been conducted in the US and the UK[6,7]. With our survey, we aim to map clinical diagnostic practices throughout Europe.

To get insight in the diversity of practices, an inquiry will be made to clinical laboratories about their methods used to measure steroid hormone levels and their BPs, reference ranges, method validation/calibration and other variables of importance. Using the results of this survey, we aim to harmonize diagnostic efforts in steroid hormonology in the future, using an evidence-based approach.

This survey is part of a larger project funded by research foundation Flanders (FWO): *'Better estimates of hormonal exposure to improve diagnosis and treatment in endocrine diseases (BEED-ED).'* The BEED-ED project aims to improve accuracy, accessibility and therefore clinical applicability of (free) steroid hormone levels, both in the general population as well as in conditions where conventional estimations on steroid hormone bioavailability are likely to be disturbed, such as obesity and organ failure.

3.2 'Primary endpoints'

Mapping of current clinical practice on steroid diagnostics in European clinical laboratories, more specifically:

- Total testosterone
- Sex hormone-binding globulin (SHBG)
- Free testosterone
- Bioavailable testosterone

3.3 Study Design

This survey study has a non-interventional, monocentric prospective design. The survey will be conducted through Qualtrics, a licensed survey platform for which paid licenses are provided by the KU Leuven. The survey will be completed by a member of personnel of the clinical laboratory. Inquiries will only be made about available diagnostic methodology on (free) steroid measurements specified in 3.2. No patients are involved nor will any patient information be collected in this survey.

A system is embedded within Qualtrics to ensure maximum 1 *completed* attempt per participant. This will exclude double (or more) attempts from the same laboratory. However, it is possible for participants to share their unique link among their staff. In that way, multiple people can contribute to the same attempt.

4. Selection of participating clinical laboratories

4.1 Inclusion criteria

Any clinical laboratory located in a sovereign European country is eligible for participation in this study.

4.2 Exclusion criteria

No exclusion criteria have been defined.

5. Ethics and regulatory approvals

The study will be conducted in compliance with the principles of the Declaration of Helsinki (7th version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents were submitted for review to Ethics Committee Research UZ/KU Leuven, Herestraat 49, 3000 Leuven. The Ethics Committee did not have any objections to the project. This project does not fall within the scope of the law of 7 May 2004. Any subsequent protocol amendments will be submitted to the same authority for approval.

The study will be conducted only on the basis of prior informed consent by the participants, or their legal representatives, to participate in the study. The principal investigator and sub-investigator shall obtain consent for all participants prior to their enrollment and participation in the study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The principal investigator and sub-investigator shall retain the consent in accordance with the requirements of all applicable regulatory agencies and laws.

The principal investigator and sub-investigator shall treat all information and data relating to the study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR") and the Belgian Law of July 30 2018 on the protection of natural persons with regard to the processing of personal data).

6. Data Handling and Management

Data will be collected through the Qualtrics platform. After collection, data will be transferred to OneDrive for Business in order to comply with KU Leuven policy on data handling and management. In OneDrive, data will be saved in a password-protected file. During and after completion of the project, all gathered data will be treated confidentially and stored for 10 years according to KU Leuven policy.

The survey will collect the following 'identifying' information:

- Clinical laboratory name
- Clinical laboratory geographic location (country)
- Clinical laboratory contact mail address
- Role/function of the health care professional that completes the form (e.g. laboratory manager, laboratory physician, endocrinologist, laboratory technician…)

Upon data collection, the 'identifying' information specified above will be pseudonymized by using a unique code to create a new identity for each clinical laboratory. The coding key will be stored in a password-secured document, separately from the research data. The research team will protect gathered data from disclosure outside the research according to the terms of the research protocol.

7. Financial Aspects

This study is funded by Research Foundation Flanders (FWO), division TBM (toegepast Biomedisch onderzoek met een primair maatschappelijke finaliteit). Grant number FWO-TBM - T004321N.

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