Progress in Standardization of Thyroid Function Tests

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On behalf of the IFCC C-STFT
Chaired by Prof. Dr. Linda Thienpont
www.ifcc-cstft.org

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Disclosure

Support to the UGent

Abbott Diagnostics (Abbott Park, IL, USA)
Beckman Coulter, Inc. (Brea, CA, USA)
bioMérieux s.a. (Marcy-l'Etoile, France)
DiaSorin S.p.A. (Saluggia, Italy)
Fujirebio Inc, (Tokyo, Japan)
Mindray Medical International Limited (Shenzhen, China)
Ortho-Clinical Diagnostics (Rochester, NY, USA, Buckinghamshire, UK)
Roche Diagnostics GmbH (Mannheim, Germany)
Shenzhen New Industries Biomedical Engineering Co., Ltd (SNIBE Co., Ltd, Shenzhen, China)
Sichuan Maccura Biotechnology Co., Ltd (Chengdu, China)
Siemens Healthcare Diagnostics Inc. (Deerfield, IL, USA)
Tosoh Corporation (Tokyo, Japan)

Economic impact of thyroid testing

High burden on the healthcare system

Yearly $180*10^6$ TSH- & $60*10^6$ FT4 tests performed worldwide

Testing volume might even increase

For example, recent meta-analysis links subclinical thyroid dysfunction to coronary heart disease & "all-cause" mortality#

➔Underpins the indisputable value of efforts towards thyroid testing fit to address modern clinical & public health needs

#Singh et al. Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis. Int J Cardiol 2008;125:41–8.

Benefits of using standardized assays

Fit to address modern clinical & public health needs

- Common reference intervals/clinical decision limits
- Evidence-based clinical practice guidelines
- Application of consistent standards of medical care
- Translation of research into patient care & disease prevention activities
- Electronic patient records

➔Whether these needs can be met, depends on the availability of laboratory results that are comparable over time, location & across assays

IFCC Working Group/Committee for Standardization of Thyroid Function Tests (C-STFT)

Chair: Prof. Dr. L. Thienpont

Terms of reference

- Develop reference measurement systems for free thyroid hormones and TSH
- Establish a network of competent reference laboratories
- Liaise with key stakeholders to implement traceable methods in routine clinical practice

http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-stft/

Development of a reference measurement system for FT4

Definition of the "measurand" FT4

IUPAC/IFCC format#

Component
Thyroxine(free)

Kind-of Quantity; units
amount-of-substance concentration (pmol/L)

System
Plasma/Serum under physiological conditions
(pH 7.4, 37°C)

#Thienpont et al. Measurement of free thyroxine in laboratory medicine – Proposal of measurand definition. IFCC WG-STFT. Clin Chem Lab Med 2007;45:563–4.

FT4 reference measurement procedure

International conventional reference measurement procedure (RMP)# based on

- Equilibrium dialysis (ED)
- Quantification of thyroxine in the dialysate with a "trueness-based" reference measurement procedure

➔ED ID-LC/tandem MS

NOTE
The measurand is *operationally defined* as
"Thyroxine in the dialysate from ED of serum prepared under defined conditions"

#Thienpont et al. Proposal of a candidate international conventional reference measurement procedure for free thyroxine in serum. IFCC Working Group for Standardization of Thyroid Function Tests (WG-STFT). Clin Chem Lab Med 2007;45:934-6.

FT4 reference measurement procedure

Development & validation

Van Uytfanghe K, Stöckl D, Ross HA, Thienpont LM. Use of frozen sera for FT4 standardization: investigation by equilibrium dialysis combined with isotope dilution-mass spectrometry and immunoassay. Clin Chem 2006;52:1817-21.

Van Houcke SK, Van Uytfanghe K, Shimizu E, Tani W, Umemoto M, Thienpont LM. IFCC Working Group for Standardization of Thyroid Function Tests (WG-STFT). IFCC international conventional reference procedure for the measurement of free thyroxine in serum. Clin Chem Lab Med 2011;49:1275-81.

Development of a reference measurement system for TSH

Definition of the measurand TSH

TSH analysis is "mixture"

Component#
Human TSH – intact, total, glycosylation encountered in diagnostic applications which should be specified

Kind-of quantity; units#
Arbitrary amount-of-substance concentration (mIU/L)

System#
Serum

NOTE: Definition requires that TSH assays deliver a measure for "total TSH" & measure the specified TSH-glycoforms in an equimolar way

#Thienpont et al. Traceability to a common standard for protein measurements by immunoassay for in-vitro diagnostic purposes Clin Chim Acta 2010;411:2058-61.

TSH reference material & -procedure

The problem

- IU defined by a WHO standard
- WHO IRP 80/558 (also 81/565) mixture components differ from those in serum; they, therefore, do potentially not give the same dose/response in immunoassays as TSH in its natural environment

➔Are not commutable and not suited for standardization

- Reference measurement procedure for TSH technically not to expect in the short- to midterm

➔Harmonization instead of standardization#

#Miller et al. Roadmap for Harmonization of clinical laboratory measurement procedures. Clin Chem 2011;57:1108-17.

TSH harmonization approach

Proposal by C-STFT

Statistical "all-procedure trimmed mean" (APTM)

- **From a method comparison with a clinically relevant panel**
- **With participation by (as many as possible) assays**

➔Serves as "surrogate RMP"[1]

NOTE

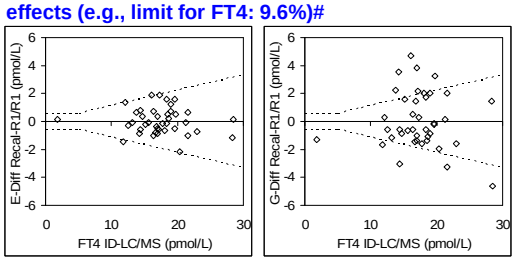
- **Statistical basis: robust factor analysis model[2]**
- **Requires excellent correlation of results to the APTM**

[1]Van Houcke et al. Harmonization of immunoassays to the all procedure trimmed mean - proof of concept by use of data from the insulin standardization project. Clin Chem Lab Med 2013;51:e103-5. doi: 10.1515/cclm-2012-0661.
[2]Stöckl et al. A statistical basis for harmonization of thyroid stimulating hormone assays using a robust factor analysis model. Clin Chem Lab Med 2014;52:965-72.

Requirements for standardization/harmonization

Sufficient intrinsic quality of performance

Total error *vs* biological limits to reflect sample-related effects (e.g., limit for FT4: 9.6%)#



Other performance attributes: imprecision, correlation, stability (within-run, between-), IQC performance

#Thienpont LM, et al. Clin Chem 2010;56:912-20.

"Step-up" approach#

Familiarization phase[1]

- **Method comparison with high-volume sera from "apparently healthy" volunteers**
- **Assessment of assays' basic performance attributes**
- **Mathematical recalibration**

First step-up[2]

- **Method comparison with a clinical panel and inclusion of master calibrators**
- **Verification that assays perform similarly on clinically relevant samples**
- **Recalibration by IVD manufacturers**

#Van Uytfanghe et al. Clin Chim Acta 2014;432:62-67.
[1]Thienpont et al. Clin Chem 2010;56:912-20.
[2]Thienpont et al. Eur Thyroid J 2014;3:109-16.

"Step-up" approach

Second step-up to standardization/harmonization

- **Method comparison with a new clinically relevant panel**
- **Technical recalibration of IVD assays**

Phase after standardization/harmonization#

- **Procure a follow-up panel**
- **Assess sustainability of the status after technical recalibration of IVD assays (= risk analysis implied by the FDA)#**
- **Prepare implementation of standardization/ harmonization**

#De Grande LA et al. Clin Chem Lab Med 2015 Jan 15 doi: 10.1515/cclm-2014-0959.

Current status of standardization of FT4 and TSH assays

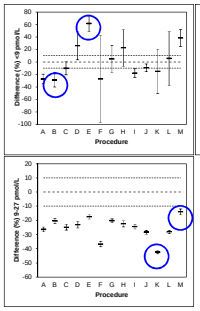
Standardization status – FT4

Phase III –
Bias to ED ID-MS#

9–27 pmol/L:
-25% (mean)
Range: -14% to -42%

>27 pmol/L:
-37% (mean)
Range: -21% to -48%

<9 pmol/L:
2% (mean)
Range: -28% to 62%



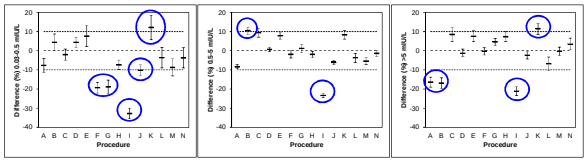
FT4 concentration range of the panel: 3 to 77 pmol/L

➔All assays strongly negatively biased

#Thienpont et al. Eur Thyroid J 2014;3:109-16.

Standardization status – TSH

Phase III – Bias to APTM#



TSH concentration range of the panel: 0.04 – 80 mIU/L

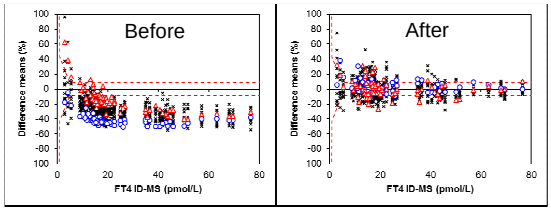
➔0.5 – 5 mIU/L: comparability quite good; only 2 assays differ by >10% from APTM
➔ <0.5 mIU/L & >5 mIU/L: max 5 out of 14 assays outside the ±10% limit
➔ Max discrepancy between assays up to ~33% (whole range)

#Thienpont et al. Eur Thyroid J 2014;3:109-16.

Feasibility of standardization/harmonization

Feasibility of standardization/recalibration

FT4 – Phase III#

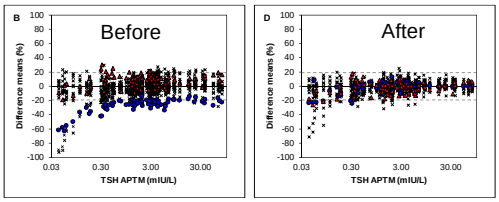


➔Bias to ED ID-LC/tandem MS removed
➔Residual dispersion nearly entirely due to within-assay effects

#Thienpont et al. Eur Thyroid J 2014;3:109-16.

Feasibility of standardization/recalibration

TSH – Phase III#



➔Recalibration nicely centers the distribution of the assay differences around zero
➔Remaining dispersion from within-assay effects
➔Indirect proof of glycosilation blind assays

#Thienpont et al. Eur Thyroid J 2014;3:109-16.

Current status of project and way forward

Step-up to standardization/harmonization

Phase IV method comparison study

- New clinically relevant panels, measured in parallel with master calibrators:
  - FT4: 4.5 – 164 pmol/L (by ED-ID/MS), n = 91
  - TSH: ~0.002 to 75 mIU/L (APTM), n = 101
- Measurements done
- Preliminary report discussed with the IVD manufacturers
- Final data treatment on-going
- Recalibration by manufacturers to follow

Preparation of follow-up panels

- TSH panel ready (and targeted)
- FT4 panel collected (will be targeted)

Proof-of-concept

Reference interval (RI)

- Panel of 120 samples from apparently healthy Americans to be measured by recalibrated assays
- FT4 target values are currently set by ED-ID/MS at UGent

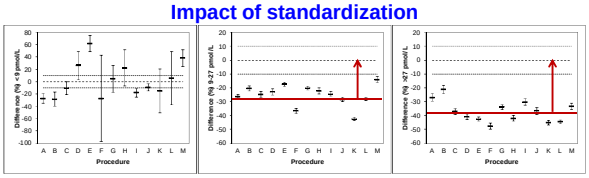
➔Proof-of-concept for success of standardization/ harmonization and feasibility to use a common RI

➔Basis for further establishment by manufacturers of new RIs after standardization/harmonization

Implementation

Obstacles to implementation

Impact of standardization



➔Most pronounced for FT4 testing

➔Effect mainly in the eu- & hyperthyroid range

➔Measurement values will increase in general by 30 – 50%

➔Reference intervals will change

Measures to waive obstacles

Prior to implementation

- Liaise with regulatory authorities
- Liaise with key stakeholders
- Do risk-benefit analysis at all levels of stakeholders
- Educate stakeholders about impact/changes
- Coordinate implementation of standardized/ harmonized assays by all manufacturers at the same point in time and worldwide
- Monitor sustainability of standardization status

Collaborating IVD manufacturers

Abbott, Beckman Coulter, bioMérieux, DiaSorin, Fujirebio, maccura, mindray, Ortho Clinical Diagnostics, Roche, Siemens Healthcare Diagnostics, Snibe, Tosoh