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Pitfalls in the measurement and interpretation of thyroid function tests☆

Olympia Koulouri, MRCP, NIHR Academic Clinical Fellow [a],
Carla Moran, MRCPI, Senior Clinical Fellow [a],
David Halsall, PhD, FRCPath, Consultant Clinical Scientist [b],
Krishna Chatterjee, FRCP, Professor of Endocrinology [a],
Mark Gurnell, PhD, FRCP, Senior Lecturer in Endocrinology & Associate Clinical Dean [a,c,*]

[a] *Metabolic Research Laboratories, Wellcome Trust – MRC Institute of Metabolic Science, University of Cambridge and National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK*
[b] *Department of Clinical Biochemistry, University of Cambridge and National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK*
[c] *School of Clinical Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK*

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Thyroid function tests (TFTs) are amongst the most commonly requested laboratory investigations in both primary and secondary care. Fortunately, most TFTs are straightforward to interpret and confirm the clinical impression of euthyroidism, hypothyroidism or hyperthyroidism. However, in an important subgroup of patients the results of TFTs can seem confusing, either by virtue of being discordant with the clinical picture or because they appear incongruent with each other [e.g. raised thyroid hormones (TH), but with non-suppressed thyrotropin (TSH); raised TSH, but with normal TH]. In such cases, it is important first to revisit the clinical context, and to consider potential confounding factors, including alterations in normal physiology (e.g. pregnancy), intercurrent (non-thyroidal) illness, and medication usage (e.g. thyroxine, amiodarone, heparin). Once these have been excluded, laboratory artefacts in commonly used TSH or TH immunoassays should be screened for, thus avoiding unnecessary further investigation and/

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* Corresponding author. Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Box 289, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK. Tel.: +44 1223 348739; Fax: +44 1223 330598.
E-mail address: mg299@medschl.cam.ac.uk (M. Gurnell).

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or treatment in cases where there is assay interference. In the remainder, consideration should be given to screening for rare genetic and acquired disorders of the hypothalamic–pituitary–thyroid (HPT) axis [e.g. resistance to thyroid hormone (RTH), thyrotropinoma (TSHoma)]. Here, we discuss the main pitfalls in the measurement and interpretation of TFTs, and propose a structured algorithm for the investigation and management of patients with anomalous/discordant TFTs.
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Introduction

Although thyroid disease in its most florid forms is easily recognised, minor perturbations of thyroid status can be more difficult to diagnose clinically, manifesting symptoms and/or signs that are non-specific (e.g. tiredness/lethargy; weight gain/loss; palpitations), and typically presenting to clinicians other than endocrinologists. Confirmation or exclusion of an underlying thyroid disorder therefore requires a high clinical index of suspicion, coupled with accurate measurement and interpretation of thyroid hormone (TH) and thyrotropin (TSH) concentrations. In the majority of cases, the results of thyroid function tests (TFTs) are straightforward, presenting a pattern that is readily recognised and consistent with the clinical impression of thyroid status. However, in a small, but significant subgroup of patients, the interpretation of TFTs is more challenging, either because the results appear discordant with the clinical picture (e.g. normal TSH in a patient with suspected thyrotoxicosis), or because different measurements appear to contradict each other (e.g. raised TH concentrations, but with non-suppressed TSH). In these patients, a structured approach to further investigation is required if resources are not to be wasted and inappropriate treatment recommended. In most instances, careful clinical reassessment of thyroid status, together with considering possible confounding factors [e.g. pregnancy, intercurrent (non-thyroidal) illness, drug therapy] readily identifies the cause of apparently anomalous/discordant TFTs. Where this is not the case, interference in one or other of TH (T4, thyroxine; T3, triiodothyronine) or TSH assays should be systematically screened for, and may require specialist laboratory work up. Thereafter, rare genetic and acquired disorders of hypothalamic–pituitary–thyroid (HPT) axis function should be considered, and referral to a specialist endocrine unit is advised. In this article we highlight the various pitfalls that can befall a clinician when faced with apparently anomalous or discordant TFTs, and show how a structured clinical approach, combined with judicious use of biochemical, radiological and genetic investigations, enables the cause of apparently confusing TFTs to be readily resolved in most cases.

General considerations when interpreting TFTs

A sound knowledge of hypothalamic–pituitary–thyroid axis physiology and the factors governing TH action at a tissue/cellular level, coupled with an understanding of the diverse array of congenital and acquired conditions that can manifest with different TFT patterns, is crucial to establishing the correct diagnosis in patients presenting with anomalous TFTs.

HPT axis physiology and TH action

TH production is tightly regulated by hypothalamic thyrotropin releasing hormone (TRH) and pituitary TSH (Fig. 1). In any given individual T4 and T3 concentrations remain relatively constant throughout life, and reflect the 'set-point' of the hypothalamic–pituitary–thyroid (HPT) axis in that individual [1]. In the euthyroid state, the thyroid gland secretes 85–90% T4 and 10–15% T3, both of which are heavily (>99.5%) protein bound to thyroxine binding globulin (TBG), albumin and transthyretin (prealbumin). Cellular entry of TH in many tissues (e.g. the brain) is dependent on specific membrane proteins [e.g. monocarboxylate transporter 8 (MCT8)] [2] (Fig. 1). These

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