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EDITORIAL

Endocrine laboratory testing: why so complex?

M. Levi

Department of Medicine, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

For a non-endocrinologist, laboratory testing involving hormones is often non-intuitive and sometimes flat-out complex. If one suspects hyperthyroidism, why not simply measure thyroid hormone? Or if a clinical suspicion of adrenal insufficiency exists, why don't we just measure plasma cortisol? The answer is simple: this approach does not work for endocrinology and a more intricate strategy is often required.

Apparently, there are several reasons that diagnostics in the world of endocrinology is less straightforward than in other areas of internal medicine. First, plasma concentrations of hormones are often extremely low. For example, plasma concentrations of insulin, free T4, or pituitary hormones are all in the picomolar range, i.e. a million times lower than that of major plasma proteins, such as albumin. It is only in the last decades that we are able to measure these small concentrations, initially by radioimmunoassays but more recently (by ever improving techniques) with more conventional enzyme-linked immunoassays. However, in the mean time we have learned to work with indirect measures of hormone activity and this may result in diagnostic strategies that have proven to work in the past, but are often not understandable at first sight for a new generation of physicians that has not grown up in times in which were not able to directly measure various hormones. However, it is not unlikely that newer diagnostic strategies will lean more strongly on direct measurements of hormones. Another difficult issue in measuring hormone concentrations is that these values are not stable over time and may rapidly fluctuate within a short time span (even within hours) due to a combination of external conditions and diurnal variation. These factors, on top of issues regarding assay variability and pre-analytical factors, render the establishment of normal values of utmost importance. In previous issues of the *Netherlands Journal of Medicine*, highly useful articles on reference values for various endocrine disorders have been published, for example on hypercortisolism and hypocortisolism, hyperprolactinaemia, hyperaldostenonism and excessive growth hormone.[1-5] These articles have proven to be useful in daily clinical practice but also in the establishment of guidelines or when reporting on individual cases in the literature.[6-9]

But apart from difficulties and solutions when measuring plasma hormone concentrations, direct measurement of hormones is often not sufficiently precise to establish a proper function or dysfunction of an endocrine axis. It is for this reason that endocrinologists often refer to function tests, which are able to provide a more dynamic answer, for example on how a target endocrine organ responds to a stimulus. In many cases, these function tests provide a more precise assessment of endocrine function and more accurately reflect the *in vivo* situation than a single measurement at a single point in time. Apparently, endocrine function is so subtle that regulatory pathways need to be challenged to provide adequate insight into their behaviour and to demonstrate endocrine derangement. But also these function tests require standardisation and proper cut-off values. In another series of articles in the *Netherlands Journal of Medicine* a number of these tests (TRH testing in hyperprolactinaemia, screening tests for hypercortisolism, and glucagon and clonidine testing in phaeochromocytoma) were extensively evaluated.[10-12] In this issue of the Journal a fourth paper on the application of the prolonged fasting test in the diagnosis of insulinoma is added.[13] Van Bon *et al*. clearly report on the utility of the prolonged fasting test for the detection of hypoglycaemia, due to insulinoma and also in patients who do not have this disease but display a surprisingly low glucose level without a proper explanation.

Standardisation and proper evaluation of diagnostic tests often receives less attention than evaluation of therapeutic interventions, which is an unwanted situation. In recent years a framework for proper assessment of diagnostic tests has been developed.[14] Briefly, tests should be standardised and validated and factors influencing the variability of the results should be understood. In addition, reference values for relevant populations should be assessed and the reliability of the test in terms of diagnostic power should be established. Furthermore, it should be evaluated whether

the test adds anything of value beyond information that is already available, e.g. from history, physical examination and other laboratory tests or imaging techniques. Ultimately, an assessment should be made whether the test result will have therapeutic or other clinically important consequences. The series of articles on endocrine testing in the *Netherlands Journal of Medicine* in recent years will certainly prove helpful in fulfilling all these prerequisites and may be of great relevance for endocrinologists and other internists.

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