Raising awareness of chronic measurement error intrinsic to immunoassay measurements of small molecule analytes

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In the recently published methodology editorial, 'Measurement error in clinical research, yes it matters', authors Groenwold *et al.* raise concerns about how measurement error and misclassification can affect the validity of biomedical studies (1). In their editorial, Groenwold *et al.* warn clinicians and researchers that bias due to error-prone data, for example drawing conclusions from a data set of 'self-reported' values as opposed to 'true' objectively measured values, lead to unsubstantiated claims in the literature. While it is absolutely essential to acknowledge that error can occur from many difficult-to-document variables such as BMIs or smoking habits, it is also important to point out that many of the so-called 'objective' laboratory measurements which are considered to be 'true' values are subject not only to bias, but far more importantly, to inaccuracy which is inherent in many immunoassays (thyroid hormones and cortisol are examples) and intrinsic to the method (IA) by which they are measured. Not only can these mistakenly 'objective' immunoassay measurements lead to unsubstantiated claims in the literature, more importantly, they frequently result in the misdiagnosis and mistreatment of patients in routine clinical practice. For example, high concentrations of cortisol binding globulin are associated with falsely low immunoassay cortisol measurements. These can lower what is a high cortisol by mass spectrometry after Synacthen stimulation (normal adrenal response) and be misinterpreted when the measured immunoassay result is falsely low suggesting adrenal insufficiency.

Over the past 30 years, our laboratory has documented significant discrepancies between the clinical presentation of patients suffering from thyroid or adrenal disorders, and the laboratory values obtained by immunoassay measurements of these analytes (2, 3, 4, 5, 6, 7, 8, 9, 10). In these cases, when liquid chromatography-tandem mass spectrometry (LC-MS/MS) was employed, the laboratory values correlated with the clinical presentations and aided in efficient diagnoses and correct treatment (11). In a recent, currently submitted for publication study, we have found that immunoassay results for small molecule hormones (thyroxine, triiodothyronine, and cortisol) are affected by both high and low concentrations of their respective binding proteins (thyroxine-binding globulin and corticosteroid-binding globulin). As binding globulin concentrations are known to vary under conditions such as pregnancy, renal diseases and the use of commonly prescribed medications such as oral contraceptives (7) and steroids, our study brings into question the accuracy of immunoassay measurements for a large population of patients (in the USA 65% of women between 15 and 49 years of age are taking oral contraceptives) (12). Moreover, some of the commonly used supplements, like biotin, interfere with immunoassays leading to false results (13).

The clinical laboratories of many institutions opt to support their endocrinology departments by providing immunoassay-testing platforms. We urge clinicians to be wary of inaccurate immunoassay values for small molecule hormones, and to advocate for LC-MS/MS testing services

for the measurement of thyroid hormones and cortisol, especially when laboratory values do not match the clinical presentation of the patient.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this letter.

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