המוגלובין מסוכרר כמדד אבחנתי לסוכרת: האם לאמץ בישראל כעת: בעד ונגד

<u>מיכה רפופורט</u>

מחלקה פנימית ג' והשרות לסוכרת, מרכז רפואי אסף הרופא צריפין

המוגלובין מסוכרר (Hba1c) מקובל מזה שנים רבות כמדד מנחה טיפול בסוכרת אך לא כמדד אבחנתי. נייר העמדה העדכני לשנת 2010 של האגודה האמריקאית לסוכרת ממליץ כי רמת המוגלובין מסוכרר שווה או גדולה מ 6.5% היא אבחנתית לסוכרת.

להמוגלובין מסוכרר יש יתרונות רבים בכל הנוגע לאבחנת סוכרת. יתרונות אלו כוללים דיוק, יציבות מעבדתית וביולוגית וקשר מוכח לסיבוכי סוכרת. יחד עם זאת מדד זה אינו נעדר חסרונות ולכן אינו מייתר את המדדים האבחנתיים האחרים לסוכרת שנשארים תקפים.

הסיבה העיקרית להמלצת האגודה האמריקאית לסוכרת לכלול את רמת המוגלובין מסוכרר במדדי הסוכרת האבחנתיים היא האחידות בערכי ושיטות המעבדה שהושגה בשנים האחרונות בארצות הברית. בישראל עדיין לא הושגה האחידות הנדרשת המאפשרת שימוש במדד זה לאבחנת סוכרת. בימים אלו נעשה בישראל בשיתוף משרד הבריאות והמועצה הלאומית לסוכרת ניסיון לאמץ שיטה מעבדתית אחידה לביצוע בדיקת המוגלובין מסוכרר.

STEROID METABOLOMICS

Ze'ev Hochberg

Rappaport Family Faculty of Medicine and Research Institute, Technion, Haifa

Individual steroid metabolites have been used as disease biomarkers in monogenic diseases. Beyond their specific effects, sex steroids mineralo- and glucocorticoids affect general body habitus and body composition and determine the individual's position in the continuum of body phenotypes: man and woman, short and tall, thin and obese, muscular and flaccid, young and aged. Analyses of steroids in plasma, urine and other body fluids by gas chromatography mass spectrometry (GCMS) provide a high-throughput profile of steroids. Traditional interpretation of GCMS output involved the semi-quantitative estimation of specific metabolites, as represented by the area under the curve of specific peaks, or the ratio between peaks representing metabolites of substrate and product of given enzymes. We utilize a fully quantitative GCMS output by introducing reference curves for each of the most telling 39 metabolites. Using an all-inclusive analysis of a steroidal array in the form of a subject steroidal fingerprinting, patients are stratified by their unique steroidal fingerprinting, and fingerprints are clustered according to specific clinical conditions. Thus, a subject's fingerprint is his unique profile of all 39 (and potentially 60) metabolites we currently quantify, and is a mark of his/her unique phenotype. To identify signatures of complex diseases, we use the steroid metabolome, which is fingerprinting-based. Bioinformatic methods and tools for data mining have been borrowed from microarray analyses, evaluating and generating disease signatures from subjects' steroidal fingerprints.

ASSESSMENT OF CORTISOL SECRETION IN VARIOUS BODY FLUIDS: "PITFALLS AND TECHNICAL ASPECTS"

Rona Limor, Naftali Stern

Department of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

Despite a wealth of apparently well-validated means of testing, the detection of diminished function of the hypothalamic pituitary adrenal axis (HPA) continues to challenge practicing clinicians. Inevitable variation exists not only in the outcome of different types of testing, but also in the ever changing methodology, antibodies and equipment used in commercial assays, leading to further variation in the proposed cutoff cortisol levels predicting normalcy. Despite these limitations and the growing understanding that normal levels of cortisol during dynamic testing should be applied in an assay and laboratory-dependent fashion, the cutoff levels for cortisol in the ACTH tests have remained unchanged over the years in clinical practice.

On the average, more than 90% of serum cortisol is protein-bound, and changes in binding proteins can alter measured serum total cortisol without influencing free concentrations of this hormone. Although total cortisol generally correlates well with the free fraction, there are clinical conditions such as major surgery, severe illness, acute phase of septic shock and stress in which large changes in cortisol binding globulin (CBG) and albumin concentration take place, thus raising a real need for measurement of free cortisol concentration. In our laboratory, we are measured bound and free cortisol in various body fluids.

Salivary cortisol is unaffected by cortisol binding globulin (CBG) and hence, allows to bypass CBG- related variations in serum total cortisol. The measurement of salivary cortisol offers a simple, stress-free and convenient, though indirect, method to assess circulating cortisol and particularly serum free cortisol levels. The expression of 11beta dehydrogenase in the parotid gland is a source of potential serum unrelated regulation of salivary cortisol. In this context, the direct measurement of serum free cortisol by equilibrium dialysis may refine the interpretation of the 1 □g ACTH test and allow further insight not afforded by testing based on serum total cortisol alone. The best index of increase adrenal glucocorticoid secretion is urinary free cortisol (UFC) measurements performed using a 24-h urine collection.

The measurement of free urinary cortisol is also one of the most useful screening tests for Cushing's syndrome. It well known that immunoassays currently employed by most clinical laboratories have significant limitations, especially concerning specificity and steroid / steroid interference. The immunoassays for UFC are using liquid–liquid extraction to eliminate interfering compounds, but are still susceptible to interferences from cortisone and/or other endogenous steroid metabolites and synthetic glucocorticoids, such as prednisolone. Another limitation of immunoassays is the lack of an internal standard to monitor variable recovery of cortisol in the extraction process. These limitations of immunoassays for UFC have led to the development of more specific methods based on liquid chromatography

with ultraviolet detection (LC-UV), liquid chromatography– mass spectrometry (LC-MS), and gas chromatography– mass spectrometry (GC-MS) The chromatographic methods not only have reduced interference for cortisol quantification, but also allow quantification of cortisone, an endogenous metabolite of UFC.

HORMONE ASSAYS: ARE THEY RELIABLE?

Varda Nadler

Maccabi Healthcare Services Central Laboratory, Rehovot, Israel

Hormone assays nowadays are mostly performed by immunoassay methods on automatic analyzers. These have the advantage of high specificity, sensitivity and precision, high throughput and low cost.

Sometimes, albeit rarely, a hormone result might be inaccurate due to analytic, pre-analytic or post-analytic factors. Some common analytical factors are:

1. Assay interference: immunoassays are susceptible to four classes of assay interference: (a) crossreactivity problems, (b) auto-antibodies to the analyte, (c) heterophilic or animal antibody interference with assay reagents and (d) in vivo or in vitro drug interactions

2. Hormone molecular heterogeneity: different variants of hormone molecules (HCG for example) might be detected differently by various assays and yield confounding results.

3. Assay standardization: most hormones lack international reference standard (IRP) preparations and therefore various immunoassays may yield dissimilar results.

4. Free thyroid hormone immunoassays appear sensitive to alterations in serum albumin, binding proteins and free fatty acid (FFA).

It is most difficult for the laboratory to proactively detect an inaccurate result from a single measurement. The physician should suspect an analytical problem when a reported value is inconsistent with the clinical status of the patient.

Once an erroneous test result is suspected, some simple means can be applied to address the issue e.g., neutralization of heterophilic Abs with blocking agent, dilution of the sample or use a different assay. In cases where analyte-Ab interference are suspected, precautions such as measuring Ab presence can be taken, as is routinely done in the case of Thyroglobulin.

None of the above, however, would identify all cases and guarantee a "true" result.