Clinical Chemistry

December 2015 Audio Summary

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On the cover this month, *Flexing Bicep*. A muscle this size conjures up thoughts of lots of testosterone. Although testosterone is associated with sexual differentiation and development, it can also be associated with a number of chronic diseases. Many laboratories are switching from immunoassay to LC-MS/MS for measuring testosterone since immunoassays have cross-reactivity issues and cannot quantify the lower concentrations observed in women and children. Yet, questions remain about how the various LC-MS/MS assays compare and what concentrations are representative of the general population, especially women, children, and non-Hispanic Asians. This issue of *Clinical Chemistry* contains two articles that address these issues. The first article is a comparison study of seven published LC-MS/MS methods for the simultaneous measurement of testosterone, androstenedione, and dehydroepiandrosterone in serum. The second article reports on the serum total testosterone concentrations in the US household population from the NHANES 2011–2012 study population, measured with standardized LC-MS/MS.

Optimizing Early Rule-Out Strategies for Acute Myocardial Infarction: Utility of 1-Hour Copeptin
By Petra Hillinger, et al.

In a prospective multicenter study, high-sensitivity cardiac troponin and copeptin were measured at presentation and after one hour in patients with suspected acute myocardial infarction. The authors hypothesized that a second copeptin measurement would facilitate early rule-out of acute myocardial infarction. 1-hour copeptin was found to neither increase the safety of the rule-out process in patients presenting with low high-sensitivity cardiac troponin and copeptin concentrations, nor increase the negative predictive value in patients presenting with low high-sensitivity cardiac troponin but increased copeptin concentrations. These findings extend previous observations regarding the reciprocal kinetics of copeptin and cardiac troponin and do not support routine use of repeated copeptin measurements for the rule-out of acute myocardial infarction.

Comparison of 7 Published LC-MS/MS Methods for the Simultaneous Measurement of Testosterone, Androstenedione, and Dehydroepiandrosterone in Serum
By Rahel M Büttler, et al.

Recently, the *Journal of Clinical Endocrinology and Metabolism* stated that sex steroids should be measured by LC-tandem mass spectrometry since it was assumed that this method is superior to immunoassays. Information on the mutual agreement of LC-tandem mass spectrometry methods, however, is scarce. In this study the authors compared seven LC-tandem mass spectrometry methods for the simultaneous measurement of testosterone, androstenedione and dehydroepiandrosterone. The methods investigated showed a reasonable agreement. However, there appeared to be differences in standardization between some of the assays and some of the assays showed a high variation. These findings stress the importance of a very critical view of the quality of LC-tandem mass spectrometry methods.

Effect of Vitamin D or Activated Vitamin D on Circulating 1,25-Dihydroxyvitamin D Concentrations: A Systematic Review and Metaanalysis of Randomized Controlled Trials
By Armin Zittermann, et al.

Evidence is accumulating that circulating 1,25-dihydroxyvitamin D levels are inversely related to short and mid-term mortality. This study reports a meta-analysis of randomized controlled trials to investigate the effect of use of vitamin D or activated vitamin D on circulating 1,25-dihydroxyvitamin D levels. The study results demonstrate that both vitamin D and activated vitamin D increase circulating 1,25-dihydroxyvitamin D significantly. In vitamin D users, however, this increase is suppressed by calcium co-administration. Some heterogeneity in study results could also be explained by the method of measuring circulating 1,25-dihydroxyvitamin D, indicating the need for standardization of 1,25-dihydroxyvitamin D measurement.

Serum Total Testosterone Concentrations in the US Household Population from the NHANES 2011–2012 Study Population
By Hubert Vesper, et al.

This is the first study reporting nationally representative data on testosterone using a highly accurate and standardized assay. Several organizations such as the Endocrine Society and expert groups have stated the need for reliable data on testosterone levels in individuals and the general population. Testosterone was measured in NHANES using a highly accurate and standardized assay. The data suggest changes in age patterns of total testosterone concentrations in men and provide information useful for establishing reference intervals.

Long Noncoding RNAs in Urine Are Detectable and May Enable Early Detection of Acute T Cell–Mediated Rejection of Renal Allografts
By Johan M Lorenzen, et al.

Acute rejection episodes of renal allotransplants are a major risk factor of long-term graft loss. Currently, a kidney biopsy is the most precise tool to diagnose acute rejection, but owing to its invasive nature is potentially associated with severe side effects. This study provides data identifying long non-coding RNAs as specific and early markers of renal allograft rejection. The authors show that the detection of long non-coding RNAs in urine is feasible, and that levels of a specific long non-coding RNA normalized in patients with acute rejection following successful anti-rejection therapy and were predictive concerning subsequent loss of kidney function. This particular long non-coding RNA may thus be a specific marker of renal allograft rejection.

Cell-Free RNA Is a Reliable Fetoplacental Marker in Noninvasive Fetal Sex Determination
By Elke Mersy, et al.

Non-invasive genetic tests using cell-free fetal DNA are increasingly used in prenatal care. An insufficient amount of cell-free fetal DNA may degrade the reliability of these tests. A marker is therefore needed to confirm the presence of sufficient fetoplacental DNA that will be universally applicable and easy to incorporate. This study examined the use of trophoblast-derived cell-free RNA as

a feto-placental marker in non-invasive fetal sex determination. Amplification of AMELY cell-free fetal DNA was combined with multiplex one-step reverse transcription-PCR of trophoblast-derived cell-free DNA and tested in 75 pregnant women. The gender of all 75 fetuses was correctly determined. The trophoblast-derived cell-free DNA proved to be a reliable fetoplacental marker.

Prognostic Significance of High-Sensitivity Cardiac Troponin T Concentrations between the Limit of Blank and Limit of Detection in Community-Dwelling Adults: A Metaanalysis
By Ravi H. Parikh, et al.

This paper investigates the significance of low levels of circulating high sensitivity cardiac troponin T, below what is routinely presented in literature. From 10,723 participants from three large community-based studies, the Cardiovascular Health Study, Atherosclerosis Risk in Communities study, and Dallas Heart Study, the authors compared those with high sensitivity cardiac troponin T below the limit of blank (less than 3 nanograms per liter) to those with high sensitivity cardiac troponin T between the limit of blank and the limit of detection (in the range from 3-4.99 nanograms per liter). They found strong cross-sectional associations with cardiovascular risk factors and structural pathology. Meta-analysis of the three cohorts showed significant associations with incident heart failure and cardiovascular death.

Reference Values and Release Kinetics of B-Type Natriuretic Peptide Signal Peptide in Patients with Acute Myocardial Infarction
By Christoph Liebetrau, et al.

Cardiac biomarkers are used for risk stratification of patients presenting with chest pain, and a multi-marker strategy is known to improve diagnostic accuracy for acute myocardial infarction or AMI. The authors established reference values for the new biomarker BNP signal peptide and characterized the time course of changes in BNP signal peptide in patients undergoing transcoronary ablation of septal hypertrophy as a model of patients with AMI. BNP signal peptide levels increased immediately after AMI induction, providing early evidence of myocardial injury. The release kinetics of BNP signal peptide differed from those of cardiac troponin T. These findings should help in developing the diagnostic value of BNP signal peptide in early AMI.