Clinical Patient Management Requires Accurate Equimolar Testing

Patients Using Vitamin D₂ Supplements Are Most at Risk for Inaccurate 25-Hydroxyvitamin D Test Results

The role of vitamin D in bone and mineral metabolism was first discovered as a factor that could cure rickets. However, vitamin D is now recognized as a pro-hormone which has multiple roles in maintaining optimal health. More recently, several studies have suggested that vitamin D insufficiency is associated with an increasing risk of many chronic diseases including cardiovascular disease, cancer, infectious diseases and autoimmune diseases.¹

With the high prevalence of vitamin D insufficiency/deficiency in the general population, testing for total 25-Hydroxyvitamin D (25-OH D) levels has now become common clinical practice. Vitamin D deficiency is typically treated by clinicians with vitamin D₃ or D₂ supplements, while fortified foods and nutrition supplements may contain either form. To ensure accurate assessment of vitamin D sufficiency both 25-OH D₃ and 25-OH D₂ serum concentrations must be measured.¹ ²

**Australian and European Method Comparison Studies**

Ten healthy volunteers from a laboratory in France provided informed consent to receive orally 600,000 IU of vitamin D₃ (ergocalciferol) as a single vial of Sterogyl 15 “A” (DB Pharma, La Varenne Saint Hilaire, France), and serum was obtained 21 days following supplementation. Each serum sample was allowed to clot for 30 minutes at room temperature, centrifuged and separated into 1 mL aliquots. Samples were stored at -20°C, and shipped on dry ice to each study site. Total 25-OHD was measured using commercial immunoassay kits from DiaSorin (LIAISON® XL 25 OH Vitamin D TOTAL Assay) and Siemens (ADVIA Centaur® XP Vitamin D Total (VitD) assay) at a reference laboratory in Australia and at a university hospital laboratory in Europe. All tests were performed according to the manufacturer’s instructions, and none of the samples showed visible signs of hemolysis or lipemia.

25-OHD D₂, 25-OHD D₃ and total 25-OHD were measured by four different LC-MS/MS (LCMS) methods (USA Method 1, USA Method 2, Australia Method, and Europe Method). The USA and Australian methods were accredited reference laboratories, and the European method was a commercial method at a university hospital laboratory in Europe. All four LCMS methods were traceable to the NIST SRM 972 standard reference material.

**Australian and European Testing Results**

The Australia and Europe testing results returned by the DiaSorin immunoassay were averaged with 25-OHD concentrations ranging from 28.2 to 85.9 ng/mL [Mean (95% confidence interval): 65.2 (52.6-77.8) ng/mL]. The Siemens immunoassay results were also averaged with 25-OHD concentrations ranging from 37.7 to 138.3 ng/mL [97.9 (75.9-120.0) ng/mL].

The LCMS consensus values for 25-OHD D₂, 25-OHD D₃ and total 25-OHD were derived by averaging the results from the four LCMS methods. 25-OH D₂ concentrations ranged from 22.2 to 68.6 ng/mL [48.9 (38.0-59.8) ng/mL], 25-OH D₃ concentrations ranged from 12.2 to 25.9 ng/mL [17.4 (14.0-20.7) ng/mL], and total 25-OHD concentrations ranged from 34.6 to 91.0 ng/mL [66.3 (53.9-78.7) ng/mL].

The total 25-OHD concentrations from each LCMS method (USA Method 1, USA Method 2, Australia Method and Europe Method), and each immunoassay method (DiaSorin and Siemens), were compared against the LCMS consensus total 25-OHD concentrations using scatter plots with linear regression, and analyses were performed using SAINT software. The results of these analyses are shown in Table 1. The LCMS consensus concentrations (slope 1.01, -2.1% mean % difference) demonstrate similar 25-OH D₂ and 25-OH D₃ serum concentrations compared against the LCMS consensus.

![Figure 1: Linear regressions of each LCMS method and immunoassay method compared against the LCMS consensus.](image)

**Summary of Results**

Results of this study suggest the DiaSorin LIAISON® 25 OH Vitamin D TOTAL Assay does not over-estimate serum 25-OH D concentrations with samples containing endogenous 25-OH D. The DiaSorin LIAISON® 25 OH Vitamin D TOTAL Assay demonstrated similar 25-OHD serum concentrations compared against LCMS.

This study suggests that equimolar measurement is a challenge for commercial immunoassay kits, which can make it difficult for clinicians to accurately interpret and manage patients treated with vitamin D₂ supplements. Studies show the DiaSorin LIAISON® 25 OH Vitamin D TOTAL Assay is equimolar for 25-OH D₂ and 25-OH D₃.


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The Quick Guide to Laboratory Statistics and Quality Control provides instructions for medical laboratory scientists, quality assurance specialists, and directors so they can develop, modify, and validate laboratory instruments and assays to meet rigorous quality standards.

The Guide outlines ways of determining accuracy and precision among assays, statistically validating them, and examining and establishing their clinical efficacy. The Guide is also intended as a reference for product support specialists so they can place and certify newly installed instruments and purchased assays.

The Guide can be used to assist physicians, pharmacists, pathologists, physician assistants, and medical fellows, residents, and students in understanding how reliability is built into laboratory assays. Further, the Guide provides a means by which laboratory data may be “mined” to develop medical research data. The information contained in this Quick Guide also clarifies laboratory assay utilization to help predict, diagnose, and monitor therapy for clinical conditions and disease.
The LIAISON® Direct Renin assay uses chemiluminescent immunoassay (CLIA) technology for the in vitro quantitative determination of renin in human EDTA-plasma specimens. Renin measurements are used as an aid in the diagnosis and treatment of certain types of hypertension.

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<th>PRECISE</th>
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<tr>
<td>Total CV% ≤ 10%</td>
<td>Wide measuring range: 2.1-300 pg/mL</td>
<td>Time to first result:</td>
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<td>Intra-assay CV% ≤ 7%</td>
<td>Limit of Quantitation (LoQ): 2.1 pg/mL</td>
<td>40 minutes</td>
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<td>Sample Type: EDTA Plasma</td>
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Callum G. Fraser, PhD, Centre for Research into Cancer Prevention and Screening, University of Dundee, Ninewells Hospital and Medical School, Dundee, Scotland |
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The Quick Guide to Autoimmune Disease Serology is intended as a brief reference for medical residents and students, physicians, physician assistants, nurses, and medical technologists who detect and diagnose autoimmune diseases.

The signs and symptoms of many autoimmune diseases can be relatively common, thus making the diagnoses of these diseases a difficult undertaking. Many of the autoantibodies listed in this Quick Guide are only markers associated with the disease and may not be involved in the pathogenesis of the disease. In addition, many of these autoantibodies can be found in several different autoimmune diseases; therefore, their presence cannot be used for a conclusive diagnosis of any specific disease. The assay and antibody descriptions included in this Quick Guide have been significantly simplified so that they can be rapidly read, understood, and utilized.
Clinical Chemistry is pleased to announce a special upcoming theme issue on Women’s Health edited by Drs. Ann M. Gronowski, JoAnn E. Manson, Elaine R. Mardis, Samia Mora, and Catherine Y. Spong titled “Advancing Women’s Health: The Impact of Biomarkers and Genomics.” Clinical Chemistry, published by the American Association for Clinical Chemistry, is the most highly cited forum for peer-reviewed, original research in the fields of clinical chemistry and laboratory medicine.

The purpose of this issue is to highlight recent advances in biochemical and genetic markers used for the diagnosis, therapy, and preventive care of women during all stages of life. This issue will include diverse themes such as cancer, cardiovascular disease, osteoporosis, metabolic disease, normal and abnormal pregnancy, infertility, and infectious disease.

Clinical Chemistry invites authors to submit original articles related to women’s health to be considered for publication in this special issue.

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- The effect of gender on the risk factors and outcomes related to diabetes, obesity, and cardiovascular disease
- Changes in the microbiome and biomarkers related to pregnancy
- Novel molecular diagnostic tools for pre-implantation genetic analysis
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- Novel biomarkers for the diagnosis of pregnancy-related disorders such as pre-eclampsia, ectopic pregnancy, preterm delivery, and gestational diabetes
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Christopher P. Price and Andrew St John

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