This issue has ramifications for patient safety. For example, our third patient presented to the emergency department with epigastric abdominal pain. After the spurious ethanol was reported, a presumptive diagnosis of alcoholic gastritis was made, and the diagnosis of acetaminophen toxicity and therapy with N-acetylcysteine was substantially delayed.

Until the manufacturer can address this issue, we have implemented a policy requiring alanine aminotransferase (ALT) to be measured in all patients with ethanol concentrations >5 mmol/L. Out of concern that hepatocellular necrosis may cause spurious ethanol elevation, when the ALT is >500 U/L, we refer the specimen to another local hospital for ethanol analysis using their Dade Behring RXL MAX to get a rapid preliminary confirmation and by gas chromatography (GC) for a final confirmation. Our experience serves as a reminder that laboratories should inquire how the manufacturers of their ethanol assays have addressed the issue of dehydrogenase interference.

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References


Angineh Gharapetian1
Daniel T. Holmes2*
Frances Rosenberg2

1 University of British Columbia
Undergraduate Program
Faculty of Medicine
The University of British Columbia
Gordon & Leslie Diamond Health Care Centre
Vancouver, BC, Canada
2 St. Paul’s Hospital
Department of Pathology and Laboratory Medicine
The University of British Columbia
Vancouver, BC, Canada

* Address correspondence to this author at:
St. Paul’s Hospital
Department of Pathology and Laboratory Medicine
1081 Burrard St.
Vancouver, BC, V6Z 1Y6 Canada
Fax 604 806 8815
E-mail dholmes@interchange.ubc.ca

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Rapid Detection of Intact FGF-23 in Tumor Tissue from Patients with Oncogenic Osteomalacia

To the Editor:

Oncogenic osteomalacia (OOM)1 is a rare tumor-induced disease characterized by hypophosphatemia due to a decreased renal threshold of phosphate reabsorption, low 1,25-dihydroxyvitamin D concentrations, and osteomalacia (1). Determining the location of OOM tumors, which often produce excess amounts of the phosphaturic hormone fibroblast growth factor-23 (FGF-23), can be difficult, and confirmation of successful tumor removal may require prolonged postoperative observation until the return of serum indicators to reference-interval concentrations (2). Here, we report the modification of a commercially available intact FGF-23 assay (3), which enabled us to rapidly document high FGF-23 content in OOM tumor extracts. The assay takes <30 min to complete, and visual inspection of the test plate is sufficient to distinguish positive from negative samples, therefore allowing fast intraoperative assessment of FGF-23 content in OOM tumor extracts.

Tumor tissue from 6 patients with OOM was used in this study. Tumor 1 tissue was from a 63-year-old woman with biochemical abnormalities characteristic of OOM. Ten years before the current study, this patient underwent resection of a small mesenchymal tumor in the maxilla, and thereafter her blood and urine chemistry indicators returned to reference intervals. The patient again developed hypophosphatemia, however, and underwent a second operation. During this procedure, tissue from the regrown tumor was obtained for this study. We also obtained tissue from 5 tumors that have previously been described (4): tumor 2 from the mandible (mixed connective tissue tumor), tumor 3 from the thigh (angiodysplastic tumor), tumor 4 from the nose (hemangiopericytoma), tumor 5 from the thigh (hemangiopericytoma), and tumor 6 from the foot (hemangiopericytoma). All tumors had been immediately frozen after surgical removal and stored at −80°C. In healthy individuals, FGF-23 is predominantly produced by bone, and therefore bone was chosen as a
control tissue; in addition, tissue was obtained from an ovarian cancer tumor. The Partners Human Research Committee approved the use of discarded human tissue.

Small amounts of tissue (32–160 mg per tumor; Table 1) were removed from the frozen tumors and placed into 800 μL of ice-cold 0.9% NaCl containing protease inhibitors (Sigma protease inhibitor cocktail P2714, 1 μL/10 mg tissue). Tissue was crushed by hand using a pestle. In a tabletop centrifuge (Eppendorf centrifuge 5415C), samples were spun at room temperature for 1 min at 16 000g in microfuge tubes, and FGF-23 was measured in the supernatants. Extracts from the 2 control tissues and from each of the 6 tumors were measured using 2 variations of an assay for intact human FGF-23 (Immutopics) (3). The capture antibody was coated onto a 96-well plate, and the detection antibody was conjugated with horseradish peroxidase. The regular assay with an upper calibrator of 400 ng/L takes about 4 h to complete, and dilutions of tumor extract with 0 ng/L calibrator were required to yield results within the calibration curve. For the rapid assay, 3 calibrators (0, 120, and 400 ng/L) or undiluted tumor extracts were incubated with the 2 FGF-23–specific antibodies for 10 min (instead of the 3-h period used in the regular assay) on a rocking platform at room temperature. After rinsing, incubation with the horseradish peroxidase substrate was performed for 10 min (instead of 30 min), the plate was visually inspected, and photographs were taken. The absorbance at 450 nm was measured by a spectrophotometer after the addition of 50 μL of 1 mol/L sulfuric acid. When measured by regular protocol, OOM tumor extracts had intact FGF-23 concentrations of 3609 to 11 187 ng/L, whereas concentrations in extracts from bone and ovarian tumor were much lower (Table 1). The modified rapid FGF-23 assay revealed in all undiluted tumor extracts an intense signal visible to the naked eye. The highest concentration calibrator (400 ng/L) and extract from bone tissue showed only small visible signals, whereas extracts from the ovarian cancer tumor and from the 0 and 120 ng/L calibrators were in-

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tissue used for extraction, mg</th>
<th>Standard assay: intact FGF-23 concentration in 800 μL extract, ng/L</th>
<th>Rapid assay: photographs of test plate</th>
<th>Rapid assay: absorbance (450 nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Calibrator, 0 ng/L</td>
<td></td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calibrator, 120 ng/L</td>
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<td>Calibrator, 400 ng/L</td>
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<tr>
<td>Bone</td>
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<tr>
<td>Tumor 1</td>
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<td></td>
<td>0.528</td>
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<td>11 187</td>
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<td>46</td>
<td></td>
<td>0.166</td>
</tr>
</tbody>
</table>

*Photographs show the test plate of the rapid FGF-23 assay before adding sulfuric acid as well as mean absorbance for duplicate wells in the rapid assay after adding sulfuric acid. The OOM tumor extracts showed, compared to extracts from control tissues or calibrators, readily visible differences in color intensity before and after adding sulfuric acid; however, the yellow color after adding sulfuric acid was difficult to capture photographically and is therefore not shown.
Letters to the Editor

More Studies on Outcomes Using Biochemical Diagnostic Tests Are Needed: Findings from the Danish Society of Clinical Biochemistry

To the Editor:

The results of biochemical tests often lead to diagnostic and therapeutic interventions, and the real value of a test can be assessed only by taking into account the subsequent health outcomes. The importance of outcomes studies, and the challenges in performing them, was reviewed by Bruns in 2001 (1), who argued that this type of study should be performed more frequently, and that such studies should be used to determine whether new tests should be implemented in clinical practice.

To investigate the extent to which this recommendation has been realized, a working group on evidence-based clinical biochemistry established by the Danish Society of Clinical Biochemistry undertook a pilot study to record the number and type of reports of diagnostic biochemical outcome studies published from January 2005 to January 2006 in 4 medical journals: Clinical Chemistry, Clinical Chemistry and Laboratory Medicine, Lancet and the New England Journal of Medicine. To be included as an outcome study, the reported study had to be designed to investigate outcomes in relation to a clinical or an economical variable of a well-defined clinical application of a biochemical test.

To identify reports of outcome studies, 2 authors manually went through reports published in each of the journals within a 12-month period. Detailed information on original full-length reports considered diagnostic biochemical outcome studies was registered together with the total number of original articles. Technical Briefs, Letters, Short Communications, Editorials, and Reviews were not included. When there were discrepancies in report selection by the 2 authors scrutinizing the same journal issues, a consensus decision was made in the entire author group. Selected outcomes reports were classified as investigating (A) direct clinical mortality or morbidity; (B) other clinical variables such as length of hospital stay, readmission rate, or satisfaction with care; or (C) economic outcomes.

A total of 829 original articles were registered, of which only 7 studies (0.8%) were classified as diagnostic biochemical outcome studies (Table 1). Six (of 231) of these original articles were published in the New England Journal...