Serum Prostatic Specific-Antigen Concentrations in Acute Myocardial Infarction

To the Editor:
We were interested to read the recent paper by Oremek and Seiffert relating to serum PSA [1] and wish to report our preliminary findings of decreased serum PSA concentrations in men after acute myocardial infarction (AMI). Our study was prompted by questions regarding an apparently spurious result in a man whose serum PSA had been measured before and after an AMI.

We measured creatine kinase (CK) and PSA in sera from men (ages 40–75 years) on hospital days 1, 2, and 3 after AMI. CK was assayed on a Kodak (Ektachem) analyzer and PSA by the Delfia (Wallac) method; interassay CVs were <5%.

Mean serum PSA concentration was significantly lower on day 2 than either day 1 or day 3 (P < 0.05, Wilcoxon matched pairs), the difference between the serum PSA results on days 1 and 3 being not significant (Table 1). The decrease was ~20%, and CK and PSA were not significantly correlated (Spearman r = 0.26, −0.24, and −0.05 on the respective days).

These preliminary results could reflect several factors, such as thrombolysis treatment, reduced physical activity, or an acute-phase response. They add to the list of clinical situations [2,3] in which PSA measurements must be interpreted with caution.

More on Total and Bone-Specific Alkaline Phosphatase

To the Editor:
Having read with interest a recent article by Woitge et al. [1] on the clinical utility of different bone alkaline phosphatase (BAP) assays, I would like to discuss some of their findings.

1. The authors report a lack of significant differences in BAP values, as measured by IRMA (“Ostase”), between pre- and postmenopausal women. However, other groups using the same immunoassay found mean increases ranging from 43% to 104% [2–5]. This is in contrast to the authors’ proposal [1] that BAP mass and enzyme activity behave differently. The necessity for studies with larger numbers of participants is given to verify the true physiological changes.

2. Woitge et al. observed higher BAP activities in men than in premenopausal women but no significant difference in BAP mass concentrations. In contrast, my colleagues and I have found a clear sex-related difference in BAP activity [6] and mass concentrations [7]. Without stratifying the reference group according to age and menopausal status, others [5,8,9] have also reported a lack of sex-related differences in BAP mass concentrations; however, this may instead reflect a postmenopausal increase in bone turnover so that BAP concentrations in females attain the values seen in males.

3. In patients with chronic hepatic failure (and no evidence of metabolic bone disease) a BAP enzyme immunoassay (“Alkphase-B”) was the only alkaline phosphatase assay showing a lack of significant increase in BAP in women over the values seen in the male reference subjects (indicating no clinically relevant cross-reactivity of the assay) [1]. In contrast, in the scatter plots Woitge et al. presented (comparing bone-specific and total alkaline phosphatase values), the Ostase IRMA seems to better discriminate skeletal and nonskeletal diseases, particularly for total alkaline phosphatase activity concentrations within the reference range. We recently reported a cross-reactivity of 20% for BAP activity determinations (as measured by Alkphase-B) with circulating liver isoenzymes [6]—even higher than the 16% reported for Ostase [5].

4. The point in assessing the bone-specific fraction of alkaline phosphatases is to determine whether or not this advances diagnostic sensitivity. To answer this question, study of patient groups with a slight increase in bone turnover is much more suitable than examining those with a marked increase. In patients receiving renal transplants, we found that 17% of sera that were characterized by a total alkaline phosphatase activity in the upper half of the reference range showed increased BAP mass concentrations [10]. The same was true of patients after bone marrow transplantation [11]. Z-score analysis revealed a greater discriminative power for BAP than for total alkaline phosphatase in postmenopausal women [5] and in the diagnosis of bone metastases [12]. In addition, diagnostic sensitivity should always be normalized to a defined value of diagnostic specificity (e.g., 95%) to make the data more comparable.

In tumor patients with metastatic spread into bone, a greater diagnostic

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Table 1. Serum CK and PSA concentrations on days 1, 2, and 3 after AMI.

<table>
<thead>
<tr>
<th>Day postinfarct</th>
<th>Serum CK, U/L</th>
<th>Serum PSA, µg/L</th>
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<tbody>
<tr>
<td>1</td>
<td>394.4 ± 529.2</td>
<td>2.81 ± 3.05</td>
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<tr>
<td>2</td>
<td>1669.2 ± 910.7</td>
<td>2.45 ± 2.58*</td>
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<td>3</td>
<td>751.4 ± 770.5</td>
<td>2.98 ± 3.21</td>
</tr>
</tbody>
</table>

*Significantly different (P < 0.05) from day 1 and 3 postinfection results.

References
4. Martin Crook* Keith Preston Ian Lancaster
   Burnley, Lancashire, UK

*Present address and address for correspondence: Clin. Chem., 5th Floor Tower, Guy’s Hosp., London SE1 9RT, UK.

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sensitivity for total alkaline phosphatase activity than for BAP measurement (as observed by Woitge et al. [1]) may just reflect an increase of nonbone alkaline phosphatases in this patient group (as the authors admitted [1]).

References


Authors of the article referred to respond:

To the Editor:

A major point in Withold’s comments on our paper [1] is the obvious lack of significant differences in BAP concentrations between pre- and postmenopausal women, as determined by IRMA (I-BAP). In this context, one should note that comparisons between laboratory observations usually depend on the clinical characterization of the study populations. As Withold points out, Garnero et al. [2] reported an increase in serum I-BAP concentrations of 104% between pre- and postmenopausal women. However, the postmenopausal population in that specific study had osteoporosis and should therefore not be considered representative for healthy postmenopausal subjects. In fact, the same authors demonstrated a significant increase in I-BAP concentrations in osteoporotic subjects, which explains the large differences between the pre- and the postmenopausal women. Notably, the nonosteoporotic premenopausal group studied by Garnero et al. [2] had serum I-BAP concentrations within the same range as the premenopausal group in our study [1]. Also, the values for serum I-BAP in healthy postmenopausal women reported by Gonelli et al. [3] are almost identical to those seen in our postmenopausal group (11.0 ± 5.1 vs 11.0 ± 4.6). We therefore believe that the differences in results between the publications cited are mainly from differences in the study populations. Independent of these considerations, we do agree with Withold on the remaining need for studies evaluating potential discrepancies in the detection of chemical mass and enzyme activity of BAPs.

In regard to the cross-reactivity of the various anti-BAP antibodies with the circulating liver isoenzyme, we believe that even in the so-called lower range of alkaline phosphatase values, the differences between commercially available immunoassays are of no clinical relevance. Although the scatter plots in Fig. 2 of our original paper [1] may on first glance suggest that I-BAP discriminates better between nonskeletal and skeletal diseases than does BAP enzyme activity (E-BAP), this is not supported by the data set. When one calculates the correlations between serum total alkaline phosphatase (TAP) and BAP values for the lower range of serum TAP only (Fig. 1), there is virtually no difference between the two immunoassays in regard to the discrimination between skeletal and nonskeletal diseases. Thus, although the differences in cross-reactivity with the circulating liver isoenzymes (20% for E-BAP and 16% for I-BAP) may be of theoretical interest, they appear to have little impact in the routine clinical setting.

A major issue in our original publication [1] was the clinical usefulness of the new immunoassays for serum BAP. We agree with Withold that, to be able to evaluate the diagnostic sensitivity of serum BAP in comparison with serum TAP, the choice of adequate patient groups is essential. In particular, inclusion of patients with only a slight increase in bone turnover will help clarify this problem. Indeed, two of the four groups studied in our report [1] fit these criteria and would therefore be suitable for this kind of analysis, yet we did not find that measurements of serum BAP resulted in a clinically relevant improvement of diagnostic sensitivity.

As previously reported by Withold [4], only 17% of patients receiving renal transplants had serum TAP values within the reference interval but increased serum concentrations of I-BAP. In our opinion, this proportion seems rather low to justify a general use of BAP measurements, particularly when taking into consideration such factors as assay performance or cost effectiveness. Thus, automated serum TAP measurements have an interand intraassay CV usually <5% and, in Germany, cost ~$US 0.50 for a single measurement. In contrast, the as-
say protocols for the immunoassays are time consuming, the inter- and intra-assay CVs are considerably 5%, and costs exceed ~US $16 per measurement. We therefore believe that, in most clinical situations, measurement of serum TAP provides sufficient diagnostic information at a good cost–benefit ratio. However, as discussed previously [1], further studies will have to elucidate the clinical usefulness of serum BAP in serial measurements.

References

Henning W. Woitge
Markus J. Seibel*
Dept. of Med
Univ. of Heidelberg
Bergheimerstr. 58
D-69115 Heidelberg
Germany

*Author for correspondence.

Thiocyanate Interference with Nova’s Ionized Magnesium Electrode

To the Editor:

An article by Rehak et al. [1] in this issue describes an effect on the magnesium results obtained by the Nova 8 analyzer in the presence of thiocyanate. The thiocyanate was present as a result of smoking.

Thiocyanate, indeed, affects the current Nova 8 magnesium sensor. We are in the process of releasing an improved magnesium sensor to resolve this effect. The new sensor shows a decrease of 0.02 mmol/L Mg\(^{2+}\) at an activity of 0.5 mmol/L Mg\(^{2+}\) when 0.5 mmol/L thiocyanate is added to the sample. After the sensor has been in use for 6 days, the reduction in Mg\(^{2+}\) is 0.04 mmol/L. At increased Mg\(^{2+}\) (1.3 mmol/L), the effect of 0.5 mmol/L thiocyanate is the same, 0.02 mmol/L initially, but after the sensor has been in use on the system for 6 days, the effect is a decrease of 0.1 mmol/L Mg\(^{2+}\).

At 0.2 mmol/L thiocyanate, the effect initially is not measurable at either 0.5 mmol/L or 1.3 mmol/L Mg\(^{2+}\). After 6 days, Mg\(^{2+}\) activities are decreased by only 0.02 mmol/L and 0.05 mmol/L, respectively. Although the decrease does change with use life of the sensor, the decrease becomes stable after the sensor has been in use on the Nova 8 for 3 days.

We are taking the appropriate action to resolve the issues raised by Rehak et al. [1]. Additional information will be provided as we complete the introduction of this version of the sensor.

Reference

John McHale
Tech. Product Mgt. & Field Support
Nova Biomedical
200 Prospect St.
Waltham, MA 02254-9141

Relations between Intestinal Alkaline Phosphatase Activity and Insulin Secretion in Obese Patients

To the Editor:

Adult intestinal alkaline phosphatase (IAP) isoenzyme has long been known to be a minor component of serum alkaline phosphatase (ALP). On electrophoresis it migrates in the β-globulin position and is detectable at low activity (<20% of total ALP) in ~20% of sera from healthy individuals [1].
Increased IAP activity has been reported in chronic renal failure (55%), liver cirrhosis (46%), and diabetes (54%) [2]. Moreover, subjects with blood groups O and B have also been reported to have increased serum IAP activity, especially in postprandial samples after a fatty meal [3]. A high percentage of IAP-positive samples has been shown to contain an IAP “variant” form displaying similar enzymatic activity but different electrophoretic mobility [1].

We measured ALP isoenzymes in a population of healthy obese subjects (n = 76; age 40.8 ± 14.9 years, mean ± SD) periodically monitored because of familial diabetes history by means of a conventional electrophoretic method [4]. Serum IAP was present in 51% (39 of 76) of the subjects and most of these samples (29 of 39) contained the variant form of the IAP (74%). The latter form was never detectable in any IAP-negative sample, as already reported by others [2].

The IAP-positive and -negative subgroups were then compared in terms of body mass index (BMI) and some serum components (total ALP, glucose, insulin, C-peptide, triglycerides, cholesterol). Significant differences between the subject groups were apparent neither in the BMI nor in the fasting basal values. However, when the response to the standard oral glucose tolerance test (OGTT) (75 g) was considered (two-way ANOVA split-plot design), glucose (P < 0.001), insulin (P < 0.05), and C-peptide (P < 0.01) were higher in the IAP-positive groups than in the negative one (Fig. 1). Such a difference was increased when considering only the IAP variant-positive group. However, no correlation was apparent between the IAP activity and the OGTT response. On the other hand, the IAP variant activity was significantly correlated to the response of insulin to OGTT (P < 0.05, Spearman test). Despite a positive trend, no significant correlation could be proved for the glucose and C-peptide responses.

We can thus conclude that: (a) the percentage of serum IAP-positive samples in a population of obese subjects with familial diabetes history is increased (51%); (b) ~74% of the IAP-positive samples contain an IAP variant; and (c) the IAP-positive subjects, and particularly the IAP-positive/variant-positive ones, showed a significant increase in insulin secretion with respect to the IAP-negative subgroup.

Such conclusions suggest a possible linkage between IAP activity and glucose metabolism, namely, that IAP could play an important role in the fasting–feeding stages. A similar hypothesis has been formulated by other authors [5] with regard to diabetic subjects.

References

Agostino Ognibene*
Laura Pala
Gianni Messeri
Carlo Maria Rotella
Piero Berti
Lab. of Endocrinol. and Toxicol.
Azienda Ospedaliera Careggi Firenze
Firenze, Italy
Dept. of Clin. Pathophysiol.
University of Florence
Firenze, Italy

*Address correspondence to this author at: Lab. di Endocrinol., Azienda Ospedaliera Careggi, Largo Palagi 1, 50139 Firenze, Italia.