Multiple Forms of Alkaline Phosphatase in Plasma of Hemodialysis Patients

In this issue Tibi and co-workers report their study on multiple forms of alkaline phosphatase (EC 3.1.3.1) in plasma of hemodialysis patients (1). They conclude that in hemodialysis patients with an increase in total alkaline phosphatase, the concurrent measurement of γ-glutamyltransferase (EC 2.3.2.2) may help to identify whether the enzyme originates from liver or bone. However, because this approach wrongly identifies the source of above-normal total alkaline phosphatase activity in more than 10% of patients, the authors recommend a separate measurement of bone isoenzyme alkaline phosphatase in hemodialysis patients.

Their paper raises a question about the value of determining isoenzymes of alkaline phosphatase in certain clinical settings, particularly in patients on dialysis. There are numerous reasons to differentiate alkaline phosphatases in the serum of these patients.

Dialysis patients suffer from a variety of bone disorders, including hyperparathyroid osteopathy, aluminum-induced bone disease, adynamic bone disease resulting from aluminum and (or) iron overload, vitamin D-induced low bone turnover, and osteosclerosis (2, 3). Some of these disorders are associated with an increase of bone alkaline phosphatase in serum; others, with a decrease.

A decrease of alkaline phosphatase, most likely bone alkaline phosphatase, is indicative of over-treatment with vitamin D (4). Recently we described the prevalence of low activities of bone alkaline phosphatase (<5th percentile of a normal matched population) in 45% of the patients undergoing hemodialysis (5).

Liver disease is a common cause of increased alkaline phosphatase in sera of dialysis patients. Although in recent years the introduction of vaccination against hepatitis B and, more recently, the use of erythropoietin have decreased dramatically the liver damage observed in hemodialysis patients, most dialysis centers are still confronted with patients presenting iron overload (hemosiderosis, hemochromatosis) and post-hepatic cirrhosis. Moreover, because cancer is more prevalent in patients with end-stage renal failure (6), liver metastasis is frequently observed in the older dialysis population. These liver diseases may be associated with either an increase of liver alkaline phosphatase, in the case of acute hepatitis; the appearance of high-Μ, alkaline phosphatase, as an early sign of liver metastasis or cholestasis (7); or an increase in intestinal alkaline phosphatase, in patients of B or O blood group with cirrhosis (8). Sometimes these responses may occur in the absence of an increase of total serum alkaline phosphatase.

The increase of intestinal alkaline phosphatase in hemodialysis patients has been known since 1974 (9, 10) and confirmed by others (11, 12). The exact mechanism of this phenomenon is unknown and the question remains open as to whether it is attributable to an increase in the synthesis of intestinal alkaline phosphatase and its release into the serum, or to a decrease in the metabolic clearance rate of this enzyme. Recently, intestinal alkaline phosphatase was also found at the brush border of proximal tubular cells (S3-segment) of the human kidney (13). However, we consider it highly unlikely that this localization plays a role in the increased intestinal alkaline phosphatase found in sera of patients with end-stage renal failure. Indeed, its location at the luminal site of the proximal tubular cells and the important loss of enzymatic activity in the fibrotic sclerotic kidneys in end-stage renal failure almost exclude the kidney as the source of serum intestinal alkaline phosphatase in these patients. In particular, because some anephric patients had serum alkaline phosphatase with a predominance of what appeared to be the intestinal isoenzyme, the renal origin could not be supported further (12).

In the most attractive hypothesis to explain these phenomena, the metabolic clearance rate of intestinal alkaline phosphatase, very high in patients with normal liver function and decreased in cirrhotic patients, is thought to be decreased in hemodialysis patients because of a loss of receptors for asialoglycoproteins, e.g., intestinal alkaline phosphatase, at the hepatocyte plasma membrane (14, 15).

Immunoglobulin-bound alkaline phosphatase was described several years ago (16, 17). Until now, except for patients with chronic inflammatory bowel disease (18), no clinical condition has been associated with alkaline phosphatase–immunoglobulin complexes. In a group of 47 hemodialysis patients, three had an immunoglobulin-bound alkaline phosphatase (tissue-nonspecific in two, intestinal alkaline phosphatase in one), accompanying a slightly increased concentration of total alkaline phosphatase in their sera (5). Undoubtedly, differentiation of isoenzymes of alkaline phosphatase is of interest in many clinical conditions (19), particularly in a population of hemodialysis patients with the various clinical settings observed for them as described above and influencing one or more of those isoenzymes.

The main problem continues to be the labor-intensive nature of available and recently developed differentiation techniques (20, 21), compared with determinations of total alkaline phosphatase combined with other liver-function tests such as γ-glutamyltransferase and 5'-nucleotidase. In addition, the important clinical and biochemical knowledge needed for the interpretation of the isoenzyme patterns limits their usefulness in the routine clinical biochemistry laboratory. We believe, however, that methods soon will be available for the identification and determination of the isoenzymes of...
alkaline phosphatase through a combination of electrophoretic separation, monoclonal antibodies, and incubation with neuraminidase, backed by an expert system (22). These should produce highly relevant clinical information in several categories of patient care.

References

Marc E. De Broe
Viviane O. Van Hoof

Departments of Nephrology–Hypertension and Clinical Chemistry
University of Antwerp
p/a University Hospital Antwerp
Wilrijkstraat 10
B-2650 Edegem/Antwerp
Belgium