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THYROXINE-BINDING GLOBULIN, HYPERTHYROXINEMIA AND HEPATOCELLULAR CARCINOMA

Huang M-J, Liaw Y-F. Thyroxine-binding globulin in patients with chronic hepatitis B virus infection: different implications in hepatitis and hepatocellular carcinoma. Am J Gastroentol 1990;85:281-284.

ABSTRACT

To determine serum thyroxine-binding globulin (TBG) levels, we used radioimmunoassay, and compared the results obtained with other tests in 231 patients with chronic hepatitis B virus infection to evaluate its clinical implications. All of these patients were hepatitis B surface antigen (HBsAg)-positive. Among them, 38 patients had hepatocellular carcinoma (HCC), 18 had chronic persistent hepatitis, 70 had chronic lobular or active hepatitis (grouped as CAH), 31 had active cirrhosis (AC), 25 had inactive cirrhosis, 20 had decompensated cirrhosis, and 29 were "healthy" HBsAg carriers. Twenty-seven patients with acute hepatitis, 12 with cancer metastasis to the liver, and 81 normal adults served as disease or normal controls. The results showed that serum TBG level increased significantly in patients with CAH, AC, or HCC. Serum TBG did not correlate with albumin or bilirubin level, but correlated with alanine aminotransferase (ALT) positively in patients with CAH ($p < 0.001$) and negatively in patients with HCC ($p < 0.01$) (slope difference $p < 0.05$). Serial determination of serum TBG and ALT also showed parallel changes in 15 patients with CAH, but not in nine patients with HCC. In contrast, the fall and rise of serum TBG levels in patients with HCC coincided with tumor resection and recurrence. The data suggest that serum TBG elevation in patients with hepatitis activity is the result of hepatocellular damage, whereas that in patients with HCC is due to increased synthesis. Whether serum TBG elevation without concomitant rise of ALT could be used as a marker of HCC awaits further study.

COMMENTS

The article under comment focuses attention on the relevance in HCC of thyroxine-binding globulin (TBG), the major transport protein of thyroxine (T_4) in human plasma. In addition, a recent case report describes a patient with HCC in whom greatly raised serum T4 levels were responsible for weight loss and weakness that had been attributed initially to hyperthyroidism (1). The patient was, however, euthyroid clinically, and hyperthyroidism was excluded by the finding of a normal-free T4 index and a low triiodothyronine (T_3) resin uptake and 24-hr ^{131}I uptake by the thyroid gland. The serum level of thyroid-stimulating hormone (TSH) was normal. A high concentration of TBG was measured in the patient's serum, and the euthyroid hyperthyroxinemia was ascribed to increased binding of T_4 to this protein.

When larger numbers of patients with HCC are studied, it becomes evident that raised serum T_4 concentrations are not uncommon. Seven of 39 of our patients (18%) (2) had a raised level, as did 22% (12 of 59) of those of Alexopoulos et al. (3). These patients, too, were euthyroid clinically and had normal-free T_4 indices, low T_3 resin uptakes, normal serum TSH concentrations and raised serum TBG levels. Although the cause of the high serum concentration of TBG in patients with HCC has not been established with certainty, the protein is almost certainly synthesized and secreted by the malignant hepatocytes (2). TBG is normally derived from hepatocytes (4), and HCC cells growing in tissue culture have been shown to produce the globulin (5). Apart from HCC, other causes of increased hepatic secretion of TBG are congenital, increased serum estrogen levels and various forms of benign hepatic disease (6). A high circulating level of the binding protein is the most common explanation for euthyroid hyperthyroxinemia. The number of patients with increased TBG values in our series (2) and that of Alexopoulos et al. (3) was 17 (44%) and 15 (25%), respectively. Thus T_4 levels are less often raised in patients with HCC and elevated serum TBG levels than would be expected. A probable explanation for this phenomenon is suggested by the finding of a reduced mean T_4 TBG ratio in such patients (2), indicating a lesser affinity of binding of T_4 to the TBG produced by malignant hepatocytes.

Ironically, in the only reported situation of a patient with both HCC and hyperthyroidism, although the serum TBG concentration was elevated, free T_4 and T_3 levels were increased, and circulating levels of TSH were inappropriately raised (7). The hyperthyroidism was attributed to ectopic synthesis by the tumor of a substance that stimulated the release of TSH from the pituitary gland.

Huang and Liaw found that 71% of 38 patients with HCC had raised serum TBG levels. With this prevalence, and the 69% reported by Terui et al. (8), it has, not surprisingly, been suggested that TBG be used as a serum marker for this tumor. In other published series, however, lower prevalences—25% (3), 32% (9) and 44% (2)—were recorded. Thus the sensitivity of TBG as a marker for HCC falls far short of that of α-fetoprotein and of other tumor markers such as des-γ-carboxy prothrombin and tumor-specific isoenzymes of γ-glutamyltransferase. Moreover, increased serum concentrations of TBG often occur in a variety

of benign hepatic diseases characterized by parenchymal inflammation, including acute hepatitis, CAH, cirrhosis and PBC. For example, Huang and Liaw found raised TBG levels in 80% of patients with CAH and 71% of those with posthepatitic cirrhosis. The high serum levels of the binding protein in these conditions parallel those of the aminotransferases, implying that TBG leaks into the circulation from damaged hepatocytes. Because cirrhosis is one of the more important disorders to be differentiated from HCC, the specificity of TBG as a marker of this tumor might also be questioned. As reported by Huang and Liaw and ourselves (2), cirrhotic patients with inactive cirrhosis (i.e., with normal serum aminotransferase levels) are known to have normal serum TBG levels. Because HCC usually coexists with inactive rather than active cirrhosis, Huang and Liaw propose that a raised serum TBG value in *a patient with a normal ALT level* may be a useful marker of HCC.

Another possible role for TBG in the diagnosis of HCC arises from the observations of Alexopoulos et al. (3). In long-term monitoring of cirrhotic patients they observed that for those patients in whom HCC developed, the serum TBG concentration rose, whereas for those patients in whom HCC did not develop, the level remained the same or even decreased. The raised TBG values preceded the clinical recognition of the tumor and in some cases even an increase in the serum α-fetoprotein level. They have therefore suggested that serum TBG may be of value in the early recognition of HCC arising in a cirrhotic liver.

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Reviews Elsewhere

***Taylor CW.* The role of G proteins in transmembrane signalling. Biochem J 1990;272:1-3.**

This review deals with intracellular signal mechanisms, specifically with signalling pathways that involve G proteins. Comparisons are established between pathways involving G proteins and simpler pathways.

***Tiribelli C, Lunazzi GC, Sottocasa GL.* Biochemical and molecular aspects of the hepatic uptake of organic anions. Biochim Biophys Acta 1990;1031:261-275.**

This review describes transport systems in the liver with special emphasis on bile acids, fatty acids, sulfobromophthalein/bilirubin and organic anions–membrane-binding proteins. Comparisons among receptors are established, and modulation of transport is discussed.

***Ford JM, Hait WN.* Pharmacology of drugs that alter multidrug resistance in cancer. Pharmacol Rev 1990;42:155-200.**

This provides a very complete review of multidrug-resistance phenotype including pharmacological, molecular biological and clinical aspects.

***Ockner RK.* Historic overview of studies on fatty acid–binding proteins. Mol Cell Biochem 1990; 98:3-9.**

This review describes the studies leading to the identification of the cytosolic fatty-acid–binding proteins (FABP) in intestinal mucosa. The review also discusses the expression of FABP in other tissues, the FABP genes, the members of the FABP family and their biological role.