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Clinical Application of Serum Bile Acid Measurement

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ABSTRACT. The diagnostic usefulness of fasting total serum bile acids (SBA) in assessment of hepatic function alterations were evaluated in 30 healthy subjects and 57 patients with obstructive jaundice. The values of SBA were compared with standard liver function tests. SBA can be used as an additional liver function test.

Keywords: Serum bile acids, Liver function, Obstructive jaundice.

Introduction

Serum bile acid levels (SBA) mirror an intricate interplay of liver and intestine, linked by the biliary and the vascular system, comprising synthesis and secretion, concentration and dilution, uptake and clearance[1].

Therefore, disturbances of bile acid metabolism must be expected not only in liver disease, but also in disorders of the biliary tract and the intestine; and by impairment of the portal circulation, too.

In patients with liver diseases all phases of bile acid metabolism are probably altered. These include uptake and bile acid synthesis, conjugation, intracellular transport and secretion into the bile.

The synthesis of bile acids is changed in liver diseases both quantitatively and qualitatively. Vlagcevec *et al.* and others authors[2,3,4,] have shown that in liver cirrhosis, where the abnormalities of bile acid metabolism have been explored in greater depth

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than other forms of chronic or acute liver disease, the synthesis of cholic acid is markedly decreased (up to 75%), while chenodeoxycholic acid synthesis is virtually unchanged. This profound decrease of cholic acid synthesis is the principal factor for the reduction of the bile acid pool to nearly half of the normal level in cirrhosis (1.2 vs 2.2g) [5].

The conjugation of bile acids with glycine or taurine may also be changed in liver disease with intra- or extrahepatic cholestasis. However, no significant correlation has been observed between the degree of liver disease and the glycine/taurine ratio[6].

Bile secretion is a particularly vulnerable hepatic function. Therefore, it is impaired in a variety of liver diseases. At the cellular level, there may be various primary sites of injury: the sinusoidal or the canalicular portion of the plasma membrane may be in disarray; the intracellular transport may be inhibited, and eventually, the pericellular permeability may possibly be altered.

In liver disease, the hepatic clearance of bile acids is impaired. Matern *et al.*[7] found that, in cirrhosis, the extraction of conjugated cholic acid decreased to 30%, and that of conjugated deoxycholic acid decreased to as little as 17%. Consequently, bile acids in serum are found to have higher fasting levels, steeper postprandial increase and a higher total postprandial elevation, when expressed as the area under the curve.

The determination of SBA was claimed to be more specific than the conventional laboratory liver function tests[8,9] and as sensitive as the bromsulfalien retention test and the indocyanine green clearance test for the detection of liver diseases[10]. The measurement of SBA levels after gallbladder contraction has been reported also to further increase diagnostic sensitivity of the test [11], mainly for the cases of anicteric liver diseases and 'minimal' liver affection[7,12]. SBA concentration has been claimed to reflect liver morphological eterations and also the seriousness of the hepatic affection[13,14,15]. SBA determination seem to have prognostic value in liver cirrhosis and it is of some value in establishing an approximate survivorship prediction in liver cirrhosis[16].

The role of SBA determination in clinical practice is still debated[17,18]. Questions arise not only because of some contradicting results[19,20] but also from a poor understanding of the pathophysiological meaning of altered levels in liver disease[21,22,23].

Therefore, this investigation evaluates the use of SBA as a liver function test for the detection of derangement in cholestasis.

Materials and Methods

Fasting sera were obtained from 57 patients with obstructive jaundice due to common bile duct stones. Diagnoses was based on clinical biochemical, and radiological grounds. The control group of subjects included 30 healthy individuals with no evidence of liver disorders on clinical examination and biochemical analysis. All patients and controls were matched for age and sex.

SBA was measured by enzymatic fluorometric method[24]. Liver function tests were

performed including total bilirubin (BIL), total proteins (TP),gamma glutamyl transpeptidase (GGT) , alkaline phosphatase (ALP), and alanine aminotransferase (ALT) by Hitachi 717 auto chemical analyzer and pseudo cholinesterase (CHE) was determined by the change in colour of the indicator bromothymol as described previously. The statistical test for significance used was Student's t-test[26].

Results

Table 1 shows the mean values of total SBA in the subjects studied. The fasting total SBA in 30 control subjects was 6.5 ± 2.1 umol/L (Mean ± SD). SBA was high in patients with obstructive jaundice: 52.4 ± 25.3 umol/L ($p < 0.0001$). Patients with obstructive jaundice had significantly raised control levels compared with normal subjects: 51.8 ± 44.0 umol/L and 13.8 ± 3.3 umol/L, respectively ($p < 0.0001$), CHE was significantly decreased in patients with obstructive jaundice as compared to controls: 4705 ± 1333 IU/L and 5799 ± 466 IU/L respectively ($p < 0.0001$). The level of ALT in controls was 19.6 ± 9.8 IU/L while in patients with obstructive jaundice was 120.1 ± 59.4 IU/L ($p < 0.0001$). The level of ALP was significantly elevated, as expected, in patients with obstructive jaundice than in control subjects: 205.02 ± 115.76 and 64.7 ± 16.7 IU/L, respectively ($p < 0.0001$). Also GGT was significantly elevated in patients with obstructive jaundice than in control group 114.9 ± 63.8 and 20.1 ± 6.9 IU/L, respectively ($p < 0.0001$). Serum TP level in control group was 71.5 ± 7.1 g/L and 61.9 ± 15.0 g/L in patients with obstructive jaundice ($p < 0.0001$).

The relationship between SBA and other liver function tests were calculated using two-tailed two-sample analysis[26] in 57 patients with cholestasis and is shown in Table 1. SBA did not correlate well with TP and CHE. The correlation between SBA and both BIL and gamma GGT was significant but was weak with both ALT and ALP.

In search of a relationship between SBA and CHE (Fig. 1) it was found that many determinations were dropped in the upper right quadrant in which SBA is elevated and CHE is normal. In contrast, in the lower left quadrant, only one specimen was observed. These facts indicate that SBA is more specific and sensitive than CHE in obstructive jaundice (Fig. 2). But on examining the correlation between SBA and other liver function tests it was observed that nearly SBA is as sensitive as BIL, ALT, APL and GGT (Fig. 2,3,4,5,).

Discussion

The raised levels of SBA in cholestasis may reflect failure of clearance which may be accompanied by hepatic necrosis. All of the patients studied except one had high SBA levels with abnormal levels of other liver function tests which is in agreement with other investigators[27].

Kadohara *et al.*[28], noticed impaired clearance of SBA in liver cirrhosis and it was closely related to the extent, form and location of oesophageal varies.

SBA correlate well with BIL and GGT. Chen *et al.*[29], found that SBA correlated

TABLE 1. Fasting serum bile acids and other liver function tests (mean ± SD) in normal subjects and in patients with obstructive jaundice.

	SBA µmol/l	BIL µmol/l	CHE IU/L	ALT IU/L	ALP IU/L	GGT IU/L	TP g/l
Control (n=30)	6.52±2.06	13.78±3.26	5799±466	19.64±9.78	64.66±16.72	20.13±6.86	71.50±7.13
Obstructive jaundice (n=57)	52.36±25.28	51.78±43.99	4705±1333	120.10±59.40	205.02±115.76	114.90±63.80	61.92±14.96
Significance (p)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.001
Correlation coeff. (SBA vs other liver function)		0.55***	0.21*	0.33**	0.41***	0.52***	0.47*

Correlation between SBA and other biochemical tests of liver function was:

* not significant

** $p < 0.05$

*** $p < 0.001$

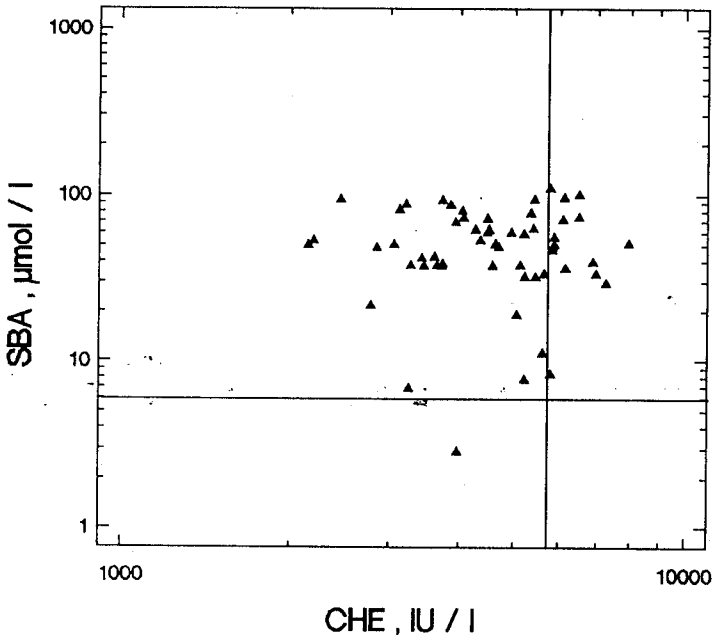

FIG. 1. Relationship between serum bile acid (SBA µmol/l) and cholinesterase (CHE IU/L) in obstructive jaundice. The vertical and horizontal lines within the X and Y axises represents the normal range for SBA and total CHE.

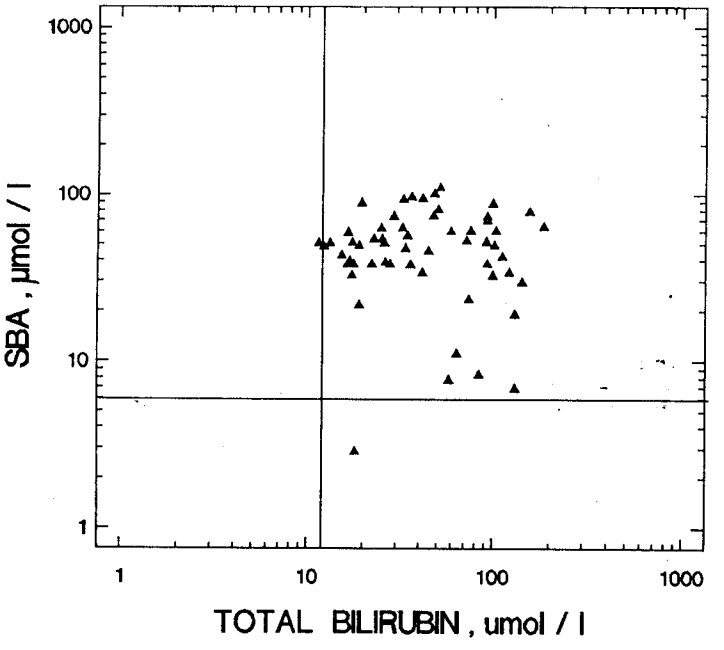

FIG. 2. Relationship between BIL (SBA µmol/L) in obstructive jaundice. The vertical and horizontal lines within the X and Y axises represent the reference range for SBA and total BIL.

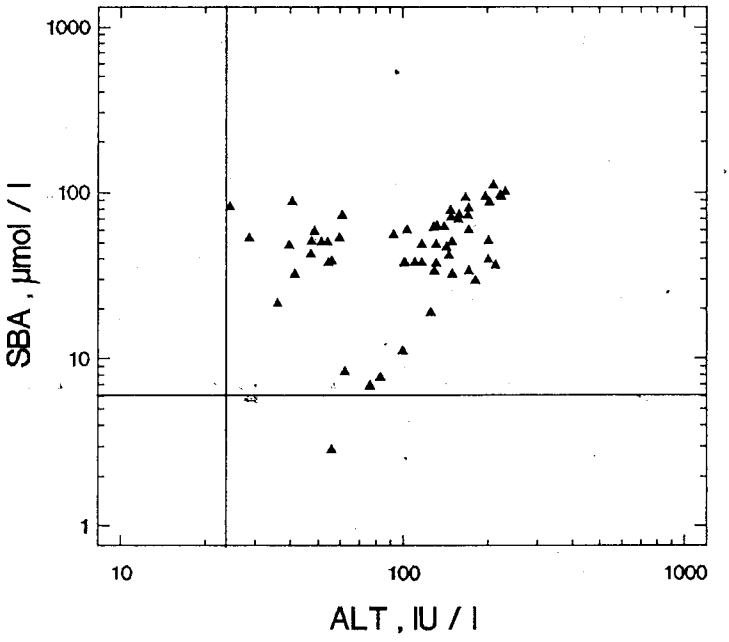

FIG. 3. Relationship between (SBA µmol/L) and (ALT IU/L) in obstructive jaundice. The vertical and horizontal lines within the X and Y axises represents the reference range for SBA and ALT.

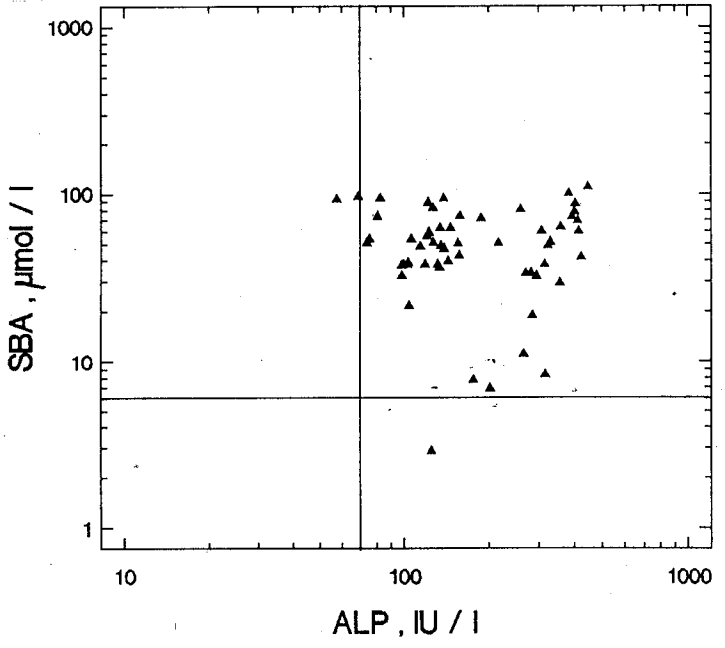

FIG. 4. Relationship between (SBA µmol/L and alkaline phosphatase (ALP IU/L) in obstructive jaundice. The vertical and horizontal lines within the X and Y axises represents the reference range for SBA and total ALP.

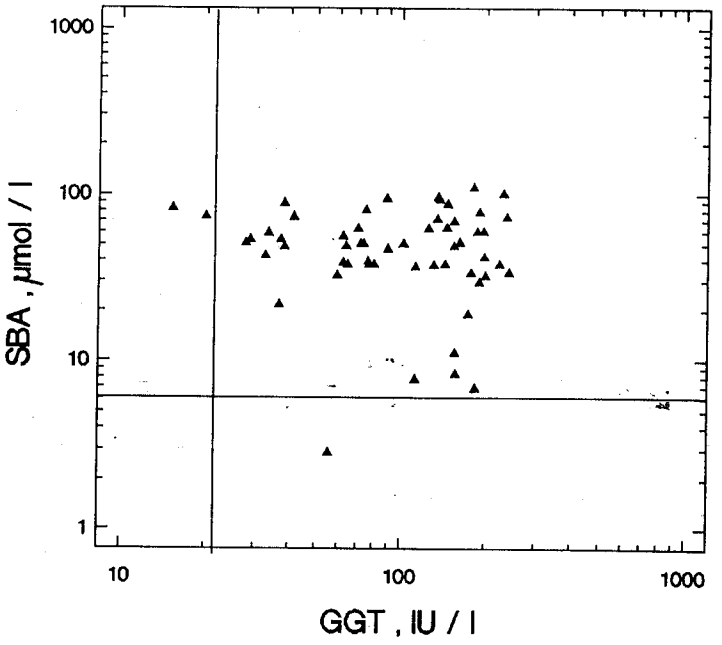

FIG. 5. Relationship between (SBA µmol/L and GGT) in obstructive jaundice. The vertical and horizontal lines within the X and Y axises represent the normal range for SBA and GGT.

well with BIL and ALT in acute and chronic hepatitis and ALP in cholangical diseases.

Osuga *et al.*[30], stated that among the conventional liver function tests, SBA correlated mostly well with serum BIL and other serum bile acids significantly correlated with indocyanin green clearance (ICG) test. Also, they observed that histologically SBA correlated with inflammation and fibrosis in chronic liver diseases. They concluded that SBA determination is a useful liver function test and considered it to reflect hepatocellular injuries like transaminase, jaundice-like bilirubin and effective hepatic flow like ICG. But Skrede *et al.*[31], failed to correlate bile acid with other liver function tests.

SBA determinations were found to be as sensitive as total BIL, ALT, and GGT. Chen *et al.*[29], claimed that SBA is more specific and sensitive than total BIL in acute hepatitis, chronic hepatitis, liver cirrhosis and hepatoma. Other investigators claimed that SBA are more specific than the conventional laboratory tests and as sensitive as bromosulfalein retention test and ICG test for detection of liver disease[32].

Ferraris *et al.*[33], compared the diagnostic value of SBA determination and conjugated cholic acids (CCA) with that of routine liver function tests in patients with liver diseases. SBA was found significantly more sensitive but less specific than CCA. Aspartate aminotransferase was nearly as sensitive as SBA.

Cravetto *et al.*[34], evaluated the diagnostic utility of the SBA for both the detection of the disease and the assessment of the liver function impairment and he concluded that

SBA determination is a highly specific but less sensitive test for the detection of liver diseases and they are not reliable in the assessment of the severity of liver function alterations.

From the above it can be concluded that SBA can be used as an additional liver function test.

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الاستخـــدام الســريـري لقـياس أمـــلاح الصفـراء في المصـل لتـقيـــيم وظـائـف الكـــبد

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* قسم الكيمياء والعلوم الطبية الحيوية السريرية ، كلية الطب والعلوم الطبية و ** قسم الجراحة العامة ، مستشفى الملك عبدالعزيز الجامعي ، جامعة الملك عبد العزيز ، جـــدة ـ المملكة العربية السعودية

المستخلص : الفائدة التشخيصية لقياس أملاح الصفراء الكلي في تقييم الخلل في وظائف الكبد تم تقديرها في ٣٠ من الأصحاء ،و٥٧ من المرضى المصابين بالصفراء نتيجة الانسداد المراري. وقورنت نتائج الأملاح الصفراوية في المصل مع وظائف الكبد القياسية. وكانت هناك علاقة مشتركة بين قيم الأملاح الصفراوية مع البيلوروبين وإنزيم جاما جلوتاميل ترانسبيبتيداز وبذلك يمكن استخدام قياس أملاح الصفراء في المصل كاختبار إضافي لوظائف الكبد .