Review Article

Subnormal Serum Liver Enzyme Levels: A Review of Pathophysiology and Clinical Significance

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Abstract

Subnormal levels of liver enzymes, below the lower limit of normal on local laboratory reports, can be useful diagnostically. For instance, subnormal levels of aminotransferases can be observed in vitamin B_6 deficiency and chronic kidney disease. Subnormal alkaline phosphatase levels may indicate the presence of hypophosphatasia, Wilson's disease, deficiencies of divalent ions, or malnutrition. Subnormal levels of gamma glutamyl transferase may be seen in cases of acute intrahepatic cholestasis, the use of certain medications, and in bone disease. Finally, subnormal levels of 5'-nucleotidase have been reported in lead poisoning and nonspherocytic hemolytic anemia. The aim of this review is to bring attention to the fact that subnormal levels of these enzymes should not be ignored as they may indicate pathological conditions and provide a means of early diagnosis.

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Introduction

Liver disease is often detected using automated assays of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) and 5'-nucleotidase (5'-NT). In particular, AST and ALT have been used to detect and monitor hepatocellular injury. ALP, GGT, and 5'-NT have also been used as markers of bile duct injury and cholestasis. In most cases, the clinical significance of the tests is based on the association of disease with elevation of serum levels.[1–3] However, it is not widely appreciated that some diseases are also associated with subnormal test results, defined as values below the lower limit of normal on local laboratory reports (Table 1). The aim of this article is to review the latest information on diseases, especially liver diseases, associated with subnormal liver enzyme levels. We also provide updates on the current knowledge of pathogenesis, specificity, and treatment of the associated conditions.

Aminotransferases

ALT, an intracellular enzyme formerly known as serum glutamate pyruvate transaminase, is found abundantly in the cytosol of hepatocytes, with an activity about 3,000 times greater than serum activity. Only small quantities of enzyme are normally present extracellularly and in serum. As a consequence of high levels relative to other organs, ALT is considered more specific to the liver than AST. However, it can also be detected in renal, cardiac, and skeletal muscle tissue. The half-life of ALT released into the blood from these sources has been reported to be 47 ± 10 h. This can result in a variation in levels of 10–30% from day to day and up to 45% within 24 h.[4,5]

Current upper limits of normal for ALT levels have been set by individual laboratories and range from 30 to 50 U/L in studies conducted over the past 10 years.[6–8] There are many factors that could be involved in normal variations in ALT levels. For example, age and sex have been reported to be associated with differences in ALT activity, as levels tend to be higher in men than women.[9–13] This finding has led several liver societies to recommend separate sex-based upper limits of normal. Ethnic differences in ALT levels have also been observed.[14]

AST exists as two genetically and immunologically distinct isoenzymes, namely cytoplasmic AST and mitochondrial AST.[15] Both isoenzymes catalyze the same reaction albeit with different kinetics and share a sequence homology of approximately 45%. While ALT is present only in cytoplasm, AST is present in both cytoplasm and mitochondria. This difference in distribution may explain the observed higher AST/ALT ratio in alcoholic liver injury, which is known to be associated with severe damage to mitochondria.[16–18] However, prolonged survival of mitochondrial AST released due to damage by alcohol or pyridoxal-6-phosphate deficiency may also be involved.[17]

Normal physiology of aminotransferases

ALT and AST catalyze the reversible transfer of amino groups

Table 1. Summary of subnormal serum enzymes and associated diseases

Subnormal serum enzyme	Associated disease
Aminotransferase (AST, ALT)	Pyridoxal 5-phosphate (vitamin B6) deficiency, alcoholic liver disease, Celiac disease, Crohn's disease, chronic kidney disease (CKD), massive acute liver injury
Alkaline phosphatase (ALP)	ALP mutations, Wilson's disease, divalent ion deficiencies, malnutrition
Gamma glutamyl transpeptidase (GGT)	Acute intrahepatic cholestasis, clofibrate drug reaction, bone disease
5'-nucleotidase (5'-NT)	Lead poisoning, nonspherocytic hemolytic anemia

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

from L-alanine and L-aspartate to L-glutamate, and produce pyruvate and oxaloacetate (Fig. 1). ALT is a component in the alanine–glucose cycle converting pyruvate to alanine in muscle, and alanine back to pyruvate to make glucose in the liver. This system is especially important for glucose regulation during stressful conditions such as fasting or vigorous exercise. It has also been suggested that the mitochondrial isoform of ALT is particularly important in gluconeogenesis in some cases.[19] AST controls the NAD+/NADH ratio in cells by taking part in the malate-aspartate shuttle in which NADH is oxidized. The reduced NAD+ in the mitochondrial matrix is involved in glycolysis and electron transport.[19,20]

Causes of subnormal aminotransferases

Pyridoxal 5'-phosphate (PLP) (vitamin B6) deficiency

PLP is the biologically active form of vitamin B6 which exists as pyridoxine in plants and as pyridoxal and pyridoxamine in animals. These substances can also exist in their respective phosphorylated forms and can be converted, primarily in the liver, to PLP, an active cofactor essential for a number of enzyme-catalyzed reactions. Both ALT and AST require PLP for their activity.

Alcoholic liver disease: PLP deficiency is common in alcoholics with or without liver disease.[21] Plasma PLP values ≤4 ng/mL have been reported in 57% of alcoholic patients with no evident hepatic or hematologic manifestations.[22] The incidence of vitamin B6 deficiency has been reported to range from 80–100% in alcoholic patients with liver disease. Serum AST and ALT tend to be normal or mildly elevated in patients with alcoholic liver disease but below 300 U/mL despite severe liver injury.[4,23–25] This may be because of the dependence of aminotransferases on PLP for their activity. Therefore, damage to hepatocytes in the presence of PLP deficiency could lower the activity of aminotransferases re-
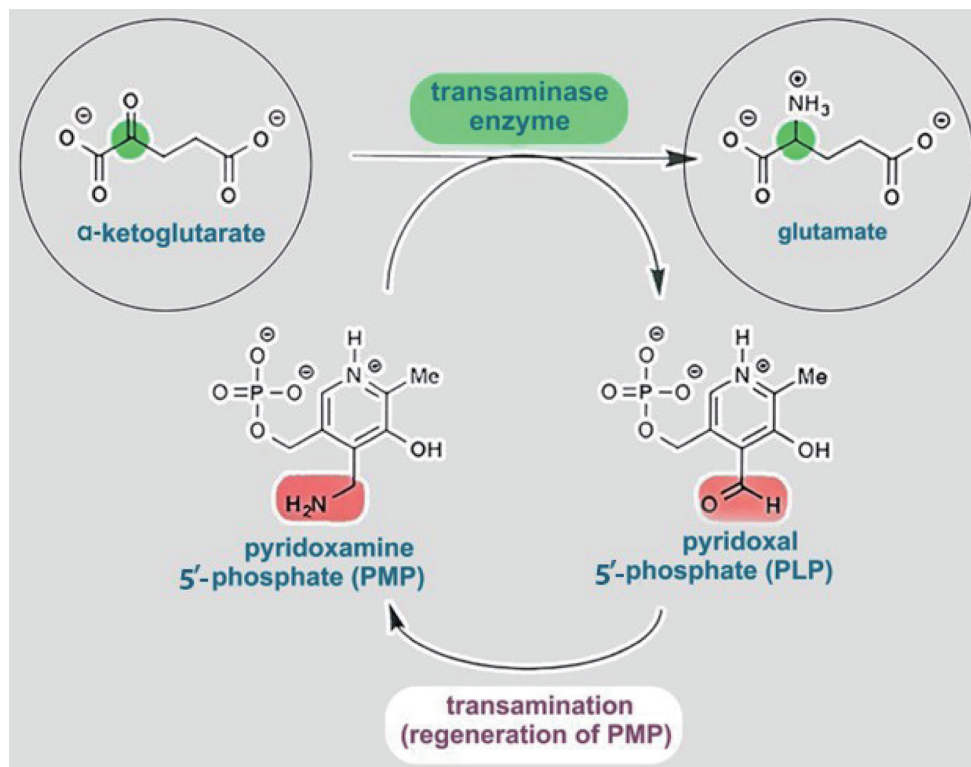
Fig. 1. A Diagram of pyridoxal phosphate transamination pathways. Pyridoxal phosphate accepts amino groups from aspartate catalyzed by aspartate aminotransferase, and alanine catalyzed by alanine aminotransferase to form Schiff's base intermediates that are subsequently reduced to form pyridoxamine phosphate. The latter then donates an amino group to an alpha-keto acid, alpha-ketoglutarate, to form an amino acid–pyridoxal 5'-phosphate Schiff's base intermediate that is then reduced to form glutamate.

leased into the circulation.[4,26] PLP deficiency has also been reported to be caused by displacement of pyridoxal phosphate from circulating albumin by acetaldehyde (an alcohol metabolite), which increases urinary excretion.[27] Decreased PLP levels may also be due to decreased intestinal absorption of vitamin B_6, as humans and other mammals cannot synthesize the vitamin. The intestine, therefore, plays a central role in maintaining and regulating normal vitamin B_6 homeostasis.[28,29]

Celiac disease: Celiac disease is an autoimmune condition characterized by intolerance to gluten, a protein present in certain grains. It is now recognized as a common disorder with prevalence estimated at 0.5–1% in different regions of the world. It is more frequently diagnosed in women than in men, with a ratio of approximately 2:1.[30,31] In patients with classic manifestations of celiac disease, malabsorption leading to potential micronutrient deficiencies is often observed.[31,32] The primary site of impact is the small intestine, where poor absorption of various nutrients including vitamin B_6 can occur.[33,34] Moreover, the main treatment for celiac disease, a gluten-free diet, may restrict the intake of vitamin B_6-rich foods.[35] Additionally, chronic inflammation and intestinal damage associated with celiac disease can disrupt normal absorption and utilization of vitamin B_6.[36–38] Insufficient levels of vitamin B_6 can result in reduced aminotransferase activity affecting the conversion of amino acids and the synthesis of new amino acids.[39] Low vitamin B_6 levels are prevalent in celiac disease patients. A study by Wierdsma *et al*.[34] found that 14.5% of newly diagnosed adult celiac disease patients had deficient levels of vitamin B_6.

Crohn's disease: Crohn's disease is a global disease affecting over 2 million individuals in North America, 3.2 million in Europe, and millions more worldwide. In Crohn's disease, malnutrition is present in up to 85% of patients, with active small intestinal involvement causing significant absorptive mucosal damage and blind loops resulting in bacterial overgrowth.[40,41] Varying rates of vitamin B_6 deficiency have been reported in Crohn's disease patients and approximately 30% of Crohn's disease patients were found to have deficient levels of vitamin B_6.[42]

Chronic kidney disease (CKD): In patients with predialysis CKD, reduction of serum aminotransferase level has been reported to be proportional to the progression of the disease. Low vitamin B_6 levels have been reported in 14% of dialysis patients.[43] Labadarios *et al*.[39] found that 83% of patients with chronic glomerulonephritis were deficient in vitamin B_6. Busch *et al*.[44,45] found that hemodialysis patients had decreased plasma PLP levels compared with other groups and that vitamin B_6 forms were significantly affected by renal function.

Although the exact cause of subnormal serum aminotransferase levels in CKD remains controversial, possible reasons are the severity of the impairment of renal function caused by glomerular dysfunction, pyridoxine deficiency and/or the presence of an inhibitory substance in uremia.[46–48] Causes of pyridoxine deficiency have been reviewed and include low dietary intake due to anorexia or impaired ability to ingest foods that are high in nutrient content. Dietary restriction may limit foods that are high in vitamins, particularly water-soluble vitamins, because of their high potassium or phosphorus content.[49] Also, some medicines may interfere with the metabolism or actions of certain vitamins including vitamin B_6, folate, and possibly riboflavin.[50] The interfering compounds include isoniazid, thyroxine, iproniazid, theophylline, hydralazine, caffeine, penicillamine, ethanol, and oral contraceptives.

A recent study speculated that hemodilution was involved in reducing serum ALT levels in CKD.[48] The reduction could also be caused by loss of aminotransferases by filtration during hemodialysis or high lactate serum levels with consumption of NADPH resulting in subnormal aminotransferase levels.[51,52] Hemodialysis can cause increased production of hepatocyte growth factor (HGF). HGF stimulates hepatocyte mitogenesis, accelerates liver regeneration, and protects the liver from toxins.[53] During dialysis, there is a significant increase in the levels of HGF in the bloodstream. This rise in HGF is believed to be triggered by factors like interleukin-1 and tumor necrosis factor released during dialysis and can stimulate the release of HGF. In turn, HGF is believed to decrease liver enzyme levels in hemodialysis patients possibly through hepatocyte proliferation and accelerated liver repair.[53,54] Hemodialysis has also been reported to increase IFN-α production and reduce hepatitis C viremia which can decrease aminotransferase levels in the serum.[55]

Massive acute liver injury

Liver cell growth and repair are central processes in recovery of normal structure and function. If hepatocyte loss is great, there may be insufficient liver tissue to release aminotransferases, which may result in decreased instead of increased serum levels of aminotransferases.[56] It has also been reported that in fulminant hepatic failure, toxic substances released from the necrotic hepatic remnant and lack of detoxification of substances from the gut inhibit or delay liver regeneration and the recovery of hepatic function including aminotransferase production.[57] Similarly, the activity of mitochondrial, but not cytoplasmic AST, after ischemic liver injury was reported to be correlated with a decrease of total adenine nucleotides.[58]

ALP

Normal physiology of ALP

ALP is a ubiquitous membrane-bound glycoprotein that catalyzes the hydrolysis of phosphate monoesters at basic pH values.[59] It is encoded by the *ALPL* gene and exists as four isozymes, intestinal, placental, germ-cell, tissue-nonspecific, and liver/bone/kidney depending upon the site of expression.[60,61] Mammalian ALPs are zinc-containing metalloenzymes that function as dimeric molecules.[62] Three metal ions including two Zn^{2+} and one Mg^{2+} at the active site are essential for enzyme activity. The activity of liver and bone ALPs in the serum has been extensively used in routine diagnosis.

ALP in the liver and biliary system converts certain bile acid intermediates to primary bile acids essential for digestion and absorption of dietary fats.[61,63,64] Another function of ALP is in the formation and maintenance of canalicular microvilli on the surface of hepatocytes.[65] These microvilli increase the surface area of hepatocytes and assist in the excretion of bile into the bile canaliculi.[66] ALP contributes to the development and integrity of the microvilli primarily located on the canalicular membrane of hepatocytes and the apical membrane of biliary epithelial cells.[67] Normal ALP levels have been reported to range from 36–150 U/L in adults.[68] In children 2–5 years of age, the normal range is 106–261 U/L in boys and 117–281 U/L in girls. In children from 6 to 12 years of age, the normal range is 118–241 U/L in boys and 129–330 U/L in girls.[69]

Conditions associated with subnormal ALP levels

Reported causes subnormal levels of ALP include ALP mutations, Wilson's disease, malnutrition, magnesium deficiency, zinc deficiency, and a protein-free diet.

ALP mutations: Subnormal ALP levels have been reported in patients with hypophosphatasia (HPP), a rare inherited systemic metabolic disease caused by mutations of the tissue-nonspecific ALP (*TNSALP*) gene.[70] TNSALP is expressed in the liver, kidney, and bone and is responsible for dephosphorylating various substrates including inorganic pyrophosphate, PLP/vitamin B_6, and phosphoethanolamine. Mutations in *TNSALP*, whether autosomal recessive or dominant, result in different clinical presentations. The disease is characterized by subnormal ALP levels and elevated PLP and phosphoethanolamine levels.[71] In HPP, deficiency or dysfunction of TNSALP disrupts the metabolism of PLP leading to alteration of both extracellular and intracellular PLP levels. As PLP is as a required cofactor of aminotransferases, decreased availability of PLP due to TNSALP deficiency impairs the normal function of these enzymes. Consequently, this disruption can cause abnormalities of amino acid metabolism. Studies have shown that subnormal ALP activity and elevated PLP levels can indicate HPP. Schmidt *et al*.[70] found that 0.52% of subjects had signs of HPP based on subnormal ALP activity and elevated PLP laboratory values. Iqbal *et al*.[72] found that patients with skeletal disease tended to have very subnormal bone ALP activity, and that PLP levels were increased in HPP and were related to disease severity.[72] These findings suggest that subnormal ALP levels may be a useful diagnostic tool for HPP, that PLP levels may be useful in patients with a suspected diagnosis of HPP, for screening family members to detect possible heterozygotes, and to monitor response to therapy. A deficiency of TNSALP in HPP leads to decreased overall ALP activity and subnormal ALP levels. This is because TNSALP accounts for a significant percentage of total ALP activity, particularly in the extracellular environment. Reduced TNSALP activity affects the hydrolysis of phosphate esters including substrates like PLP and contributes to the decreased ALP levels observed in HPP.

Wilson's disease: Wilson's disease, or hepatolenticular degeneration, is an autosomal recessive state of copper overload characterized by serious neurological disease and development of chronic liver disease that often leads to cirrhosis.[73,74] ATP7B, encodes a P-type adenosine triphosphatase metal ion transporter that is mainly expressed in hepatocytes. It is responsible for export of copper from hepatocytes.[75–77] Abnormal function of ATP7B protein can result in reduced excretion of copper in bile, resulting in hepatic accumulation and injury. When hepatic storage capacity is exceeded, copper is transported from the liver systemically, resulting in multiorgan damage. Abnormal ATP7B protein also results in decreased incorporation of copper into ceruloplasmin. Liver disease typically begins with a presymptomatic period during which copper accumulation in the liver causes subclinical hepatitis that progresses to liver cirrhosis.[78,79]

Subnormal ALP levels have been observed in 60–90% of individuals with Wilson's disease, primarily in patients with severely impaired hepatic function.[80,81] However, subnormal ALP levels are not specific to this condition and can also be seen in other liver diseases. The mechanism of the development of subnormal ALP levels in Wilson's disease is uncertain, but some reports have suggested that zinc deficiency may be involved.[82] Subnormal ALP levels have also been correlated with the presence of Coombs (+) hemolytic anemia, but were not found to be related to excess copper per se in the bloodstream.[83]

Divalent ion deficiency: Divalent ions such as Mg^{2+}, Co^{2+}, and Mn^{2+} are activators of ALP, and Zn^{2+} is a constituent metal ion of the enzyme. A specific Mg^{2+}/Zn^{2+} ratio is necessary to avoid displacement of Mg^{2+} and to obtain optimal activity. Many studies have also shown that Zn deficiency decreases the activity of bone-related enzymes and minerals such as ALP, Ca, P and Mg.[84] Several studies suggested that magnesium and zinc ions have complex effects on ALP activity but do not directly address the effect of magnesium and zinc deficiency on ALP expression.[85,86] Others found that magnesium stabilizes the structure of ALP and regulates its catalytic activity by zinc.[87] Zinc inhibits ALP by displacing magnesium ions from its binding site.[88]

Malnutrition: Malnutrition can decrease ALP activity by several mechanisms.[89,90] These include deficiencies of proteins, vitamins, minerals, and nutrients essential for the synthesis and proper functioning of ALP. Inadequate intake of these nutrients can impair ALP production and activity.[91,92] Liver dysfunction can directly impact ALP activity. In severe cases of liver damage, ALP levels may be decreased on this basis.[93] ALP plays a role in bone mineralization and impaired bone formation due to malnutrition, which can indirectly affect ALP activity.[94] Finally, intestinal damage or inflammation caused by malnutrition can reduce ALP production leading to lower ALP levels.[95] Several studies have reported that malnutrition was associated with subnormal ALP levels. Jain *et al*.[96] found significantly decreased serum ALP levels in malnourished children compared with controls. Coward *et al*.[97] demonstrated that hypoalbuminemia which is often associated with malnutrition, contributed to subnormal ALP levels. Abiodun *et al*.[98] found decreased levels of alpha 2 HS-glycoprotein were associated with decreased ALP levels. Bandsma *et al*.[99] observed that subnormal ALP levels in severely malnourished children were related to the degree of hypoalbuminemia.[99]

GGT

Normal physiology

GGT is present in various tissues including liver, bile ducts, kidney, pancreas, and intestine. It normally collaborates with glutathione to transport peptides into the cell across the cell membrane. GGT levels in serum are mainly due to hepatobiliary contribution[100] with normal serum levels of GGT ranging from 9 to 85 U/L.[101] GGT is normally involved in the extracellular catabolism of glutathione, the major thiol antioxidant in mammalian cells. This enables precursor amino acids to be assimilated and re-utilized for intracellular synthesis of glutathione.[102] Glutathione plays a role in protecting cells against oxidants produced during normal metabolism. GGT catalyzes the transfer of a glutamyl residue (linked through glutamate gamma carboxylic acid to an amine or to another amino acid) to an acceptor,[102] thereby maintaining adequate levels of glutathione. GGT is also involved in the transfer of amino acids across cell membranes[103] and metabolism of leukotriene.[104] Serum level alone has been used to monitor cholestasis, and the ratio of GGT to bilirubin levels have been used to assess liver inflammation.[105]

Conditions associated with subnormal GGT levels

Acute intrahepatic cholestasis: Subnormal serum activity of GGT is often observed in cases of acute intrahepatic cholestasis due to various causes such as drug-induced liver injury, viral hepatitis, or autoimmune liver disease. Subnormal GGT activity has been reported to be due to a reduction in the synthesis and release of GGT from hepatocytes resulting in subnormal serum GGT activity. Kajiwaraet *et al*.[106] found that patients with acute intrahepatic cholestasis had subnormal serum GGT activity despite high bilirubin levels, suggesting that factors inhibited the release of the enzyme into the blood stream from the liver.

Clofibrate drug reaction: Clofibrate is primarily used to decrease elevated levels of triglycerides and increase levels of high-density lipoprotein cholesterol. It has been reported to decrease GGT levels in some individuals but the mechanism is not fully understood.[107] Some studies have reported that clofibrate may influence the expression and activity of enzymes involved in GGT metabolism, including glutathione-S-transferase.[107–110] In rat studies it was found that clofibrate treatment increased the levels of reduced glutathione in the liver and kidney.[111] The drug did not alter superoxide dismutase, glutathione peroxidase, glutathione reductase, or glucose-6-phosphate dehydrogenase activity in the liver and heart. However, it decreased the activity of glutathione-S-transferase in the liver and small intestine. Additionally, administration of clofibrate reduced the content of specific polypeptides associated with glutathione-S-transferase in liver cells.[111]

Bone disease: Bone remodeling is involved in determining bone mass.[112] Serum GGT levels have been reported to be inversely associated with bone mass density. Choi *et al*.[111] found that serum GGT levels were negatively associated with bone mass density even after adjusting for confounders such as alcohol consumption.[113–115] GGT has been reported to affect bone metabolism through systemic and local mechanisms.[116–119]

5'-NT

Normal physiology

5'-NT is an enzyme involved in nucleotide metabolism and it plays an important role in generating adenosine. It is expressed on the cell surface of various cell types including endothelial and immune cells and in tissues like the liver and kidney. Its main function is the hydrolysis of extracellular adenosine monophosphate into adenosine, a process vital in the purinergic signaling pathway. Adenosine is a signaling molecule that regulates inflammation, immune responses, and vascular tone. It interacts with specific receptors on the surface of immune cells and endothelial cells to modulate physiological processes such as inflammation, immune response, and dilation of blood vessels.

Conditions associated with subnormal 5'-NT levels

Lead poisoning: Lead exposure can lead to subnormal levels of 5'-NT due to direct inhibitory effects on the enzyme in serum[120,121] and red blood cells.[122] Several other mechanisms have been proposed to explain the effects of lead exposure on subnormal levels of 5'-NT. Wang *et al*.[123] found that lead exposure caused DNA and chromosome damage, and Rygiel *et al*.[124] found that prenatal lead exposure was associated with increased gene-specific 5-methylcytosine and 5-hydroxymethylcytosine levels. Increased breakdown of DNA and subsequent accumulation of pyrimidines inhibited the activity of 5'-NT. Some clinical features of lead poisoning are similar to those of certain genetic mutations that result in pyrimidine excess due to enzyme deficiency.

Nonspherocytic hemolytic anemia (NSHA)

NSHA is a member of a group of inherited disorders in which mutations or deficiencies in specific enzymes or proteins involved in red blood cell metabolism disrupt normal cell function and lead to hemolysis. Pyruvate kinase, which is essential for ATP production in red blood cells, is an enzyme that is affected in certain types of NSHA.[125–127] When pyruvate kinase is deficient or dysfunctional, there is an increased reliance on alternative pathways for energy production lead-ing to increased breakdown of ATP and subsequent accumulation of adenosine monophosphate. Elevated adenosine monophosphate levels can inhibit 5'-NT resulting in subnormal pyruvate kinase activity (126).

Summary and discussion

We included normal serum enzyme values reported in this review to provide the reader with published ranges of normal. However, because "normal" values could differ depending on the test population, the units reported, and the assays and laboratories used, we defined "subnormal" values as values below the lower limit of normal in local laboratory reports rather than specific cut off values. This was done intentionally to avoid issues of applying a single standard cutoff value across various populations and communities. Using this definition, subnormal serum aminotransferase levels can occur due a deficiency of vitamin B_6 commonly seen in alcoholic liver disease as well as in celiac disease, Crohn's disease, and CKD. In celiac and Crohn's disease, malabsorption of nutrients including vitamin B_6 may result in reduced aminotransferase levels. There may be subnormal levels of vitamin B_6 due to various factors associated with CKD. In situations where there is severe liver injury or fulminant hepatic failure, extensive loss of hepatocytes may result in decreased release of aminotransferases into the bloodstream, leading to subnormal serum levels of these enzymes. Subnormal levels of ALP may be associated with HPP, Wilson's disease, and malnutrition through various mechanisms including nutrient deficiencies and impaired bone formation. Serum GGT levels have been reported to be subnormal in acute intrahepatic cholestasis due to drug-induced liver injury, viral hepatitis, and autoimmune liver disease. Additionally, the use of clofibrate has been linked to subnormal GGT levels in some individuals. Agents that affect bone remodeling such as estrogens, vitamin D, and parathyroid hormone may also play a role in affecting GGT levels. Subnormal levels of 5'-NT have been associated with lead poisoning and NSHA (Table 1).

Conclusions

Subnormal levels of liver-associated enzymes including aminotransferases, ALP, GGT, and 5'-NT can be associated with disease. Because assays of these enzymes are commonly available and frequently ordered to screen for hepatobiliary disease with elevated levels, it is important to realize that subnormal levels may also be indicative of many treatable diseases. Recognition may lead to otherwise unsuspected diagnoses and, therefore, could make possible early intervention before irreversible damage has occurred. As with any laboratory finding, laboratory errors are possible, and repeat testing should be undertaken to confirm results. Future research on the mechanisms involved in the development of subnormal serum enzyme values will be of value in understanding the pathogenesis of disease and may be helpful in improving the early diagnosis of associated diseases.

Conflict of interest

Author contributions

Study concept and design (GYW), drafting of the manuscript (EMY, GYW), literature review and writing of the manuscript (EMY), critical revision of the manuscript for important intellectual content (GYW), manuscript proofreading (GYW, EMY). All authors have made a significant contribution to this study and have approved the final manuscript.

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