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Review Article

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

Elham M. Youssef[1*] and George Y. Wu[2]

[1]*Biochemistry Department, National Research Center, Cairo, Egypt;* [2]*Department of Medicine, Division of Gastroenterology-Hepatology, University of Connecticut Health Center, Farmington, CT, USA*

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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.

**Keywords:** Transaminases; Vitamin $B_6$; Celiac disease; Renal insufficiency; Hepatolenticular Degeneration; Crohn disease; Malnutrition; Clofibrate; Bone diseases; Lead poisoning; Anemia; Hemolytic.

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; GGT, gamma glutamyl transpeptidase; HGF, hepatocyte growth factor; HPP, hypophosphatasia; NSHA, nonspherocytic hemolytic anemia; PLP, pyridoxal 5'-phosphate; *TNSALP*, tissue-nonspecific alkaline phosphatase.

[*]**Correspondence to:** Elham M. Youssef, Biochemistry Department, National Research Center, Dokki, Cairo 12622, Egypt. ORCID: https://orcid.org/0000-0003-1451-2456. Tel: +20-1006576382, Fax: +20-237601877, E-mail: elhamelabd66@gmail.com

## 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 $B_6$) 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 $B_6$) deficiency*

PLP is the biologically active form of vitamin $B_6$ 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 $B_6$ 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-

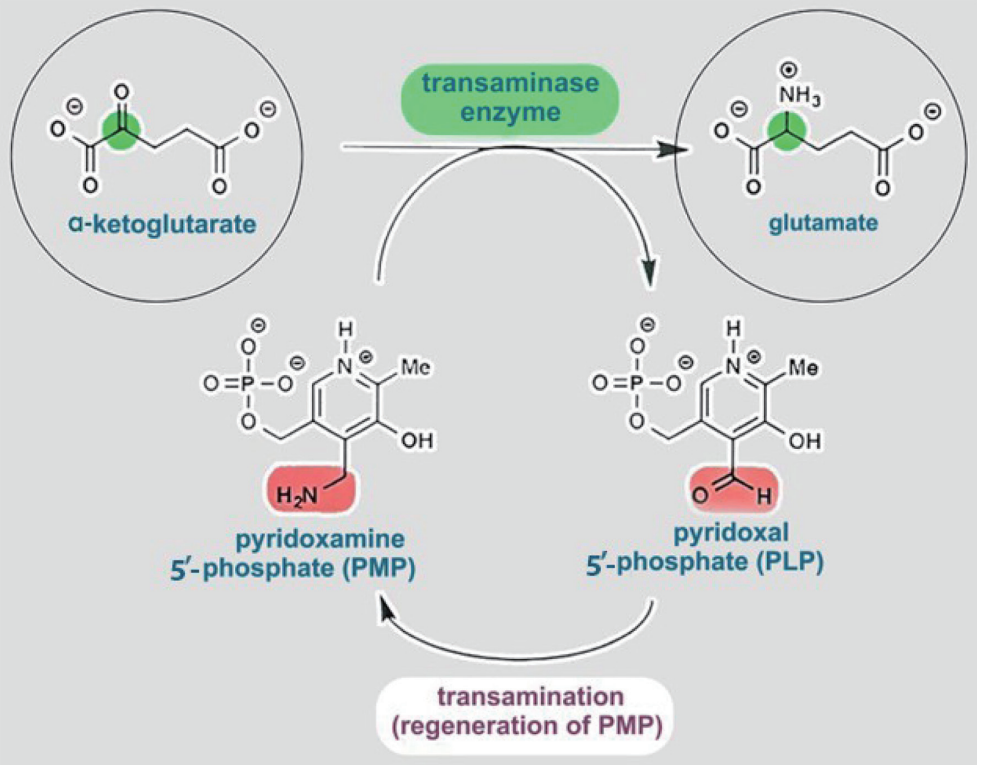


**Fig. 1. A Diagram of pyridoxal phosphate transamination pathways.** Pyridoxal phosphate accepts amino groups from aspartate catalyzed by aspartate aminotransferase, and alanine catalyzed by alanine aminotransferase to form Schiff's base intermediates that are subsequently reduced to form pyridoxamine 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 leading 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.

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## Conflict of interest

GYW has been Editor-in-Chief of *Journal of Clinical and Translational Hepatology* since 2013. The other author has no conflict of interests related to this publication.

## 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.

## References


[1] Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seeff LB. Diagnosis and monitoring of hepatic injury. II. Recommendations for use of laboratory tests in screening, diagnosis, and monitoring. Clin Chem 2000;46(12):2050–2068. doi:10.1093/clinchem/46.12.2050, PMID:11106350.

[2] Lee TH, Kim WR, Poterucha JJ. Evaluation of elevated liver enzymes. Clin Liver Dis 2012;16(2):183–198. doi:10.1016/j.cld.2012.03.006, PMID:22541694.

[3] Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med 2000;342(17):1266–1271. doi:10.1056/NEJM200004273421707, PMID:10781624.

[4] Thapa BR, Walia A. Liver function tests and their interpretation. Indian J Pediatr 2007;74(7):663–671. doi:10.1007/s12098-007-0118-7, PMID:17699976.

[5] Kim WR, Flamm SL, Di Bisceglie AM, Bodenheimer HC. Public Policy Committee of the American Association for the Study of Liver Disease. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. Hepatology 2008;47(4):1363–1370. doi:10.1002/hep.22109, PMID:18366115.

[6] Kim BK, Han KH, Ahn SH. "Normal" range of alanine aminotransferase levels for Asian population. J Gastroenterol Hepatol 2011;26(2):219–220. doi:10.1111/j.1440-1746.2010.06603.x, PMID:21261710.

[7] Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ 2004;328(7446):983. doi:10.1136/bmj.38050.593634.63, PMID:15028636.

[8] Dutta A, Saha C, Johnson CS, Chalasani N. Variability in the upper limit of normal for serum alanine aminotransferase levels: a statewide study. Hepatology 2009;50(6):1957–1962. doi:10.1002/hep.23200, PMID:19787805.

[9] Liu Z, Que S, Xu J, Peng T. Alanine aminotransferase-old biomarker and new concept: a review. Int J Med Sci 2014;11(9):925–935. doi:10.7150/ijms.8951, PMID:25013373.

[10] Poustchi H, George J, Esmaili S, Esna-Ashari F, Ardalan G, Sepanlou SG, *et al*. Gender differences in healthy ranges for serum alanine aminotransferase levels in adolescence. PLoS One 2011;6(6):e21178. doi:10.1371/journal.pone.0021178, PMID:21738618.

[11] Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, *et al*. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137(1):1–10. doi:10.7326/0003-4819-137-1-200207020-00006, PMID:12093239.

[12] Elinav E, Ben-Dov IZ, Ackerman E, Kiderman A, Glikberg F, Shapira Y, *et al*. Correlation between serum alanine aminotransferase activity and age: an inverted U curve pattern. Am J Gastroenterol 2005;100(10):2201–2204. doi:10.1111/j.1572-0241.2005.41822.x, PMID:16181369.

[13] Zhang J, Wang ZY, Zhang JP, Zhou H, Ding Z. Prevalence of Elevated Alanine Aminotransferase by Diagnostic Criterion, Age, and Gender among Adolescents. Gastroenterol Res Pract 2020;2020:4240380. doi:10.1155/2020/4240380, PMID:32411198.

[14] Varma A, Trudeau S, Zhou Y, Jafri SM, Krajenta R, Lamerato L, *et al*. African Americans Demonstrate Significantly Lower Serum Alanine Aminotransferase Compared to Non-African Americans. J Racial Ethn Health Disparities 2021;8(6):1533–1538. doi:10.1007/s40615-020-00916-2, PMID:33230736.

[15] Ndrepepa G. Aspartate aminotransferase and cardiovascular disease—a narrative review. J Lab Precis Med 2021;6(6):1–17. doi:10.21037/jlpm-20-93.

[16] Pol S, Bousquet-Lemercier B, Pave-Preux M, Pawlak A, Nalpas B, Berthelot P, *et al*. Nucleotide sequence and tissue distribution of the human mitochondrial aspartate aminotransferase mRNA. Biochem Biophys Res Commun 1988;157(3):1309–1315. doi:10.1016/s0006-291x(88)81017-9, PMID:3207426.

[17] Neupert W, Schatz G. How proteins are transported into mitochondria. Trends Biochem Sci 1981;6:1–4. doi:10.1016/0968-0004(81)90002-5.

[18] Rej R. Multiple molecular forms of human cytoplasmic aspartate aminotransferase. Clin Chim Acta 1981;112(1):1–11. doi:10.1016/0009-8981(81)90263-1, PMID:7237820.

[19] McCommis KS, Finck BN. Mitochondrial pyruvate transport: a historical perspective and future research directions. Biochem J 2015;466(3):443–454. doi:10.1042/BJ20141171, PMID:25748677.

[20] Lehninger AL. Phosphorylation coupled to oxidation of dihydrodiphosphopyridine nucleotide. J Biol Chem 1951;190(1):345–359. doi:10.1016/S0021-9258(18)56077-4, PMID:14841183.

[21] Diehl AM, Potter J, Boitnott J, Van Duyn MA, Herlong HF, Mezey E. Relationship between pyridoxal 5′-phosphate deficiency and aminotransferase levels in alcoholic hepatitis. Gastroenterology 1984;86(4):632–636. doi:10.1016/S0016-5085(84)80110-9, PMID:6698365.

[22] Leevy CM, Moroianu SA. Nutritional aspects of alcoholic liver disease. Clin Liver Dis 2005;9(1):67–81. doi:10.1016/j.cld.2004.11.003, PMID:15763230.

[23] Mezey E. Liver disease and nutrition. Gastroenterology 1978;74(4):770–783. doi:10.1016/0016-5085(78)90259-7, PMID:344129.

[24] Majumdar S, Shaw G, O'gorman P, Aps E, Offerman E, Thomson A. Blood vitamin status (B1, B2, B6, folic acid and B12) in patients with alcoholic liver disease. Gastroenterology 1982;52(3):266–271. PMID:7174224.

[25] Sullivan MK, Daher HB, Rockey DC. Normal or near normal aminotransferase levels in patients with alcoholic cirrhosis. Am J Med Sci 2022;363(6):484–489. doi:10.1016/j.amjms.2021.09.012, PMID:34619146.

[26] Sherman KE. Evaluation of abnormal liver tests. GI/Liver Secret. 4th ed. St. Louis (MI): Mosby; 2010.

[27] Méndez-Sánchez N, Almeda-Valdés P, Uribe M. Alcoholic liver disease. An update. Ann Hepatol 2005;4(1):32–42. doi:10.1016/S1665-2681(19)32083-6, PMID:15798659.

[28] Lieber CS. ALCOHOL: its metabolism and interaction with nutrients. Annu Rev Nutr 2000;20:395–430. doi:10.1146/annurev.nutr.20.1.395, PMID:10940340.

[29] Halsted CH. B-Vitamin dependent methionine metabolism and alcoholic liver disease. Clin Chem Lab Med 2013;51(3):457–465. doi:10.1515/cclm-2012-0308, PMID:23096111.

[30] Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. World J Gastroenterol 2012;18(42):6036–6059. doi:10.3748/wjg.v18.i42.6036, PMID:23155333.

[31] Rubin JE, Crowe SE. Celiac Disease. Ann Intern Med 2020;172(1):ITC1–ITC16. doi:10.7326/AITC202001070, PMID:31905394.

[32] Fasano A, Catassi C. Clinical practice. Celiac disease. N Engl J Med 2012;367(25):2419–2426. doi:10.1056/NEJMcp1113994, PMID:23252527.

[33] Schuppan D, Dennis MD, Kelly CP. Celiac disease: epidemiology, pathogenesis, diagnosis, and nutritional management. Nutr Clin Care 2005;8(2):54–69. PMID:16013224.

[34] Wierdsma NJ, van Bokhorst-de van der Schueren MAE, Berkenpas M, Mulder CJ, van Bodegraven AA. Vitamin and mineral deficiencies are highly prevalent in newly diagnosed celiac disease patients. Nutrients 2013;5(10):3975–3992. doi:10.3390/nu5103975, PMID:24084055.

[35] Rybicka I, Gliszczynska-Swiglo A. Gluten-Free Flours from Different Raw Materials as the Source of Vitamin B(1), B(2), B(3) and B(6). J Nutr Sci Vitaminol (Tokyo) 2017;63(2):125–132. doi:10.3177/jnsv.63.125, PMID:28552877.

[36] Lodhi MU, Stammann T, Kuzel AR, Syed IA, Ishtiaq R, Rahim M. Celiac Disease and Concomitant Conditions: A Case-based Review. Cureus 2018;10(2):e2143. doi:10.7759/cureus.2143, PMID:29632752.

[37] Zali MR, Nejad MR, Rostami K, Alavian SM. Liver complications in celiac disease. Hepat Mon 2011;11(5):333–341. PMID:22087157.

[38] Schuppan D, Zimmer KP. The diagnosis and treatment of celiac disease. Dtsch Arztebl Int 2013;110(49):835–846. doi:10.3238/arztebl.2013.0835, PMID:24355936.

[39] Merrill AH Jr, Henderson JM. Diseases associated with defects in vitamin B6 metabolism or utilization. Annu Rev Nutr 1987;7:137–156. doi:10.1146/annurev.nu.07.070187.001033, PMID:3300730.

[40] Goh J, O'Morain CA. Review article: nutrition and adult inflammatory bowel disease. Aliment Pharmacol Ther 2003;17(3):307–320. doi:10.1046/j.1365-2036.2003.01482.x, PMID:12562443.

[41] Rana SV, Bhardwaj SB. Small intestinal bacterial overgrowth. Scand J Gastroenterol 2008;43(9):1030–1037. doi:10.1080/00365520801947074, PMID:18609165.

[42] Kuroki F, Iida M, Tominaga M, Matsumoto T, Hirakawa K, Sugiyama S, *et al*. Multiple vitamin status in Crohn's disease. Correlation with disease activity. Dig Dis Sci 1993;38(9):1614–1618. doi:10.1007/BF01303168, PMID:8359072.

[43] Rock CL, DeRoeck MB, Gorenflo DW, Jahnke MG, Swartz RD, Messana JM. Current prevalence of vitamin B6 deficiency in hemodialysis and peritoneal dialysis patients. J Ren Nutr 1997;7(1):10–16. doi:10.1016/S1051-2276(97)90003-0.

[44] Busch M, Göbert A, Franke S, Ott U, Gerth J, Müller A, *et al*. Vitamin B6 metabolism in chronic kidney disease—relation to transsulfuration, advanced glycation and cardiovascular disease. Nephron Clin Pract 2010;114(1):c38–c46. doi:10.1159/000245068, PMID:19816042.

[45] Chen CH, Yang WC, Hsiao YH, Huang SC, Huang YC. High homocysteine, low vitamin B-6, and increased oxidative stress are independently associated with the risk of chronic kidney disease. Nutrition 2016;32(2):236–241. doi:10.1016/j.nut.2015.08.016, PMID:26526964.

[46] Cohen GA, Goffinet JA, Donabedian RK, Conn HO. Observations on decreased serum glutamic oxalacetic transaminase (SGOT) activity in azotemic patients. Ann Intern Med 1976;84(3):275–280. doi:10.7326/0003-4819-84-3-275, PMID:1259262.

[47] Wolf PL, Williams D, Coplon N, Coulson AS. Low aspartate transaminase activity in serum of patients undergoing chronic hemodialysis. Clin Chem 1972;18(6):567–568. PMID:5026769.

[48] Rej R, Fasce Jr CF, Vanderlinde RE. Increased aspartate aminotransferase activity of serum after in vitro supplementation with pyridoxal phosphate. Clin Chem 1973;19(1):92–98. PMID:4683373.

[49] Chazot C, Steiber AL, Kopple JD. Vitamin metabolism and requirements in

chronic kidney disease and kidney failure. Nutritional Management of Renal Disease. 4th ed. Cambridge (MA): Academic Press; 2022.
[50] Steiber AL, Kopple JD. Vitamin status and needs for people with stages 3-5 chronic kidney disease. J Ren Nutr 2011;21(5):355–368. doi:10.1053/j.jrn.2010.12.004, PMID:21439853.
[51] Ono K, Ono T, Matsumata T. The pathogenesis of decreased aspartate aminotransferase and alanine aminotransferase activity in the plasma of hemodialysis patients: the role of vitamin B6 deficiency. Clin Nephrol 1995;43(6):405–408. PMID:7554526.
[52] Crawford DR, Reyna RS, Weiner MW. Effects of in vivo and in vitro dialysis on plasma transaminase activity. Nephron 1978;22(4-6):418–422. doi:10.1159/000181484, PMID:740106.
[53] Rampino T, Arbustini E, Gregorini M, Guallini P, Libetta C, Maggio M, *et al*. Hemodialysis prevents liver disease caused by hepatitis C virus: role of hepatocyte growth factor. Kidney Int 1999;56(6):2286–2291. doi:10.1046/j.1523-1755.1999.00791.x, PMID:10594807.
[54] Mizuno S, Nakamura T. Hepatocyte growth factor: a regenerative drug for acute hepatitis and liver cirrhosis. Regen Med 2007;2(2):161–170. doi:10.2217/17460751.2.2.161, PMID:17465748.
[55] Badalamenti S, Catania A, Lunghi G, Covini G, Bredi E, Brancaccio D, *et al*. Changes in viremia and circulating interferon-alpha during hemodialysis in hepatitis C virus-positive patients: only coincidental phenomena? Am J Kidney Dis 2003;42(1):143–150. doi:10.1016/s0272-6386(03)00417-7, PMID:12830466.
[56] Johnston DE. Special considerations in interpreting liver function tests. Am Fam Physician 1999;59(8):2223–2230. PMID:10221307.
[57] Gove CD, Hughes RD. Liver regeneration in relationship to acute liver failure. Gut 1991;32(Suppl):S92–S96. doi:10.1136/gut.32.suppl.s92, PMID:1916477.
[58] Nishimura T, Yoshida Y, Watanabe F, Koseki M, Nishida T, Tagawa K, *et al*. Blood level of mitochondrial aspartate aminotransferase as an indicator of the extent of ischemic necrosis of the rat liver. Hepatology 1986;6(4):701–707. doi:10.1002/hep.1840060427, PMID:2426171.
[59] Millán JL. Mammalian alkaline phosphatases: from biology to applications in medicine and biotechnology. Hoboken (NJ): J Wiley & Sons; 2006.
[60] Pankovich AM, Sclamberg EL, Stevens J. Organ-specific and cross-reacting isoenzymes in human alkaline phosphatases. Int Arch Allergy Appl Immunol 1972;43(3):401–409. doi:10.1159/000230856, PMID:4628647.
[61] Sharma U, Pal D, Prasad R. Alkaline phosphatase: an overview. Indian J Clin Biochem 2014;29(3):269–278. doi:10.1007/s12291-013-0408-y, PMID:24966474.
[62] Makris K, Mousa C, Cavalier E. Alkaline Phosphatases: Biochemistry, Functions, and Measurement. Calcif Tissue Int 2023;112(2):233–242. doi:10.1007/s00223-022-01048-x, PMID:36571614.
[63] Harris H. The human alkaline phosphatases: what we know and what we don't know. Clin Chim Acta 1990;186(2):133–150. doi:10.1016/0009-8981(90)90031-m, PMID:2178806.
[64] Buchet R, Millán JL, Magne D. Multisystemic functions of alkaline phosphatases. Methods Mol Biol 2013;1053:27–51. doi:10.1007/978-1-62703-562-0_3, PMID:23860646.
[65] Tietz P, Jefferson J, Pagano R, Larusso NF. Membrane microdomains in hepatocytes: potential target areas for proteins involved in canalicular bile secretion. J Lipid Res 2005;46(7):1426–1432. doi:10.1194/jlr.M400412-JLR200, PMID:15834130.
[66] McCuskey R. Anatomy of the liver. Hepatology: a textbook of liver disease. Amsterdam, Netherlands: Elsevier; 2012.
[67] Asada-Kubota M, Kanamura S. Intracellular localization of alkaline phosphatase in freshly isolated foetal rat hepatocytes. Histochem J 1986;18(9):500–506. doi:10.1007/BF01675618, PMID:3781878.
[68] Padilla OaA. J. Merck Manual Blood Tests: Normal Values. Available from: https://www.merckmanuals.com/professional/resources/normal-laboratory-values/commonly-used-panels.
[69] Wanjian G, Jie H, Liang G, Cheng W, Tian X, Jianjiang S, *et al*. Establishment of Reference Interval for Alkaline Phosphatase in Healthy Children of Various Ethnicities, Aged 0-12 Years. Lab Med 2017;48(2):166–171. doi:10.1093/labmed/lmx017, PMID:28340217.
[70] Schmidt T, Schmidt C, Amling M, Kramer J, Barvencik F. Prevalence of low alkaline phosphatase activity in laboratory assessment: Is hypophosphatasia an underdiagnosed disease? Orphanet J Rare Dis 2021;16(1):452. doi:10.1186/s13023-021-02084-w, PMID:34711245.
[71] Millán JL, Whyte MP. Alkaline Phosphatase and Hypophosphatasia. Calcif Tissue Int 2016;98(4):398–416. doi:10.1007/s00223-015-0079-1, PMID:26590809.
[72] Iqbal SJ, Brain A, Reynolds TM, Penny M, Holland S. Relationship between serum alkaline phosphatase and pyridoxal-5'-phosphate levels in hypophosphatasia. Clin Sci (Lond) 1998;94(2):203–206. doi:10.1042/cs0940203, PMID:9536930.
[73] Członkowska A, Litwin T, Dusek P, Ferenci P, Lutsenko S, Medici V, *et al*. Wilson disease. Nat Rev Dis Primers 2018;4(1):21. doi:10.1038/s41572-018-0018-3, PMID:30190489.
[74] Steindl P, Ferenci P, Dienes HP, Grimm G, Pabinger I, Madl C, *et al*. Wilson's disease in patients presenting with liver disease: a diagnostic challenge. Gastroenterology 1997;113(1):212–218. doi:10.1016/s0016-5085(97)70097-0, PMID:9207280.
[75] Bitter RM, Oh S, Deng Z, Rahman S, Hite RK, Yuan P. Structure of the Wilson disease copper transporter ATP7B. Sci Adv 2022;8(9):eabl5508. doi:10.1126/sciadv.abl5508, PMID:35245129.
[76] Charbonnier P, Chovelon B, Ravelet C, Ngo TD, Chevallet M, Deniaud A. ATP7B-Deficient Hepatocytes Reveal the Importance of Protein Misfolding Induced at Low Copper Concentration. Cells 2022;11(21):3400. doi:10.3390/cells11213400, PMID:36359796.
[77] Schmidt K, Ralle M, Schaffer T, Jayakanthan S, Bari B, Muchenditsi A, *et al*. ATP7A and ATP7B copper transporters have distinct functions in the regulation of neuronal dopamine-β-hydroxylase. J Biol Chem 2018;293(52):20085–20098. doi:10.1074/jbc.RA118.004889, PMID:30341172.
[78] Kasztelan-Szczerbinska B, Cichoz-Lach H. Wilson's Disease: An Update on the Diagnostic Workup and Management. J Clin Med 2021;10(21):5097. doi:10.3390/jcm10215097, PMID:34768617.
[79] Poujois A, Woimant F. Challenges in the diagnosis of Wilson disease. Ann Transl Med 2019;7(Suppl 2):S67. doi:10.21037/atm.2019.02.10, PMID:31179304.
[80] Roberts EA, Schilsky ML. A practice guideline on Wilson disease. Hepatology 2003;37(6):1475–1492. doi:10.1053/jhep.2003.50252, PMID:12774027.
[81] Socha P, Janczyk W, Dhawan A, Baumann U, D'Antiga L, Tanner S, *et al*. Wilson's Disease in Children: A Position Paper by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;66(2):334–344. doi:10.1097/MPG.0000000000001787, PMID:29341979.
[82] Sintusek P, Kyrana E, Dhawan A. Value of Serum Zinc in Diagnosing and Assessing Severity of Liver Disease in Children With Wilson Disease. J Pediatr Gastroenterol Nutr 2018;67(3):377–382. doi:10.1097/MPG.0000000000002007, PMID:29668570.
[83] Shaver WA, Bhatt H, Combes B. Low serum alkaline phosphatase activity in Wilson's disease. Hepatology 1986;6(5):859–863. doi:10.1002/hep.1840060509, PMID:3758940.
[84] Ray CS, Singh B, Jena I, Behera S, Ray S. Low alkaline phosphatase (ALP) in adult population an indicator of zinc (Zn) and magnesium (Mg) deficiency. Curr Res Nutr Food Sci J 2017;5(3):347–352. doi:10.12944/CRNFSJ.5.3.20.
[85] Przybyłkowski A, Szeligowska J, Januszewicz M, Raszeja-Wyszomirska J, Szczepankiewicz B, Nehring P, *et al*. Evaluation of liver fibrosis in patients with Wilson's disease. Eur J Gastroenterol Hepatol 2021;33(4):535–540. doi:10.1097/MEG.0000000000001754, PMID:32433421.
[86] Shribman S, Poujois A, Bandmann O, Czlonkowska A, Warner TT. Wilson's disease: update on pathogenesis, biomarkers and treatments. J Neurol Neurosurg Psychiatry 2021;92(10):1053–1061. doi:10.1136/jnnp-2021-326123, PMID:34341141.
[87] Frommer D, Morris J, Sherlock S, Abrams J, Newman S. Kayser-Fleischer-like rings in patients without Wilson's disease. Gastroenterology 1977;72(6):1331–1335. doi:10.1016/S0016-5085(77)80038-3, PMID:558126.
[88] Ciancaglini P, Pizauro JM, Curti C, Tedesco AC, Leone FA. Effect of membrane moiety and magnesium ions on the inhibition of matrix-induced alkaline phosphatase by zinc ions. Int J Biochem 1990;22(7):747–751. doi:10.1016/0020-711x(90)90010-z, PMID:2401375.
[89] DEAN RF, SCHWARTZ R. The serum chemistry in uncomplicated kwashiorkor. Br J Nutr 1953;7(1-2):131–147. doi:10.1079/bjn19530016, PMID:13032352.
[90] Edozien J. Enzymes in serum in kwashiorkor. Pediatrics 1961;27(2):325–333. PMID:13725748.
[91] Gudehithlu KP, Ramakrishnan CV. Effect of undernutrition on the chemical composition and the activity of alkaline phosphatase in soluble and particulate fractions of the newborn rat calvarium and femur. I: Effect of gestational undernutrition in the rat. Calcif Tissue Int 1990;46(6):373–377. doi:10.1007/BF02554967, PMID:2364324.
[92] Cho YE, Lomeda RA, Ryu SH, Sohn HY, Shin HI, Beattie JH, *et al*. Zinc deficiency negatively affects alkaline phosphatase and the concentration of Ca, Mg and P in rats. Nutr Res Pract 2007;1(2):113–119. doi:10.4162/nrp.2007.1.2.113, PMID:20535396.
[93] Eisenbach C, Sieg O, Stremmel W, Encke J, Merle U. Diagnostic criteria for acute liver failure due to Wilson disease. World J Gastroenterol 2007;13(11):1711–1714. doi:10.3748/wjg.v13.i11.1711, PMID:17461475.
[94] Vimalraj S. Alkaline phosphatase: Structure, expression and its function in bone mineralization. Gene 2020;754:144855. doi:10.1016/j.gene.2020.144855, PMID:32522695.
[95] Kadji Fassi JB, Boukeng Jatsa H, Membe Femoe U, Greigert V, Brunet J, Cannet C, *et al*. Protein undernutrition reduces the efficacy of praziquantel in a murine model of Schistosoma mansoni infection. PLoS Negl Trop Dis 2022;16(7):e0010249. doi:10.1371/journal.pntd.0010249, PMID:35839247.
[96] Jain A, Jadhav AA, Varma M. Relation of oxidative stress, zinc and alkaline phosphatase in protein energy malnutrition. Arch Physiol Biochem 2013;119(1):15–21. doi:10.3109/13813455.2012.737809, PMID:23373727.
[97] Thacker PA. The pig as a biomedical model to study human protein calorie malnutrition [Dissertation]. Vancouver, BC, Canada: University of British Columbia; 1978.
[98] Abiodun PO, Ihongbe JC, Dati F. Decreased levels of alpha 2 HS-glycoprotein in children with protein-energy-malnutrition. Eur J Pediatr 1985;144(4):368–369. doi:10.1007/BF00441779, PMID:3935449.
[99] Childhood Acute Illness and Nutrition (CHAIN) Network. Characterising paediatric mortality during and after acute illness in Sub-Saharan Africa and South Asia: a secondary analysis of the CHAIN cohort using a machine learning approach. EClinicalMedicine 2023;57:101838. doi:10.1016/j.eclinm.2023.101838, PMID:36825237.
[100] Gowda S, Desai PB, Hull VV, Math AA, Vernekar SN, Kulkarni SS. A review on laboratory liver function tests. Pan Afr Med J 2009;3:17. PMID:21532726.
[101] Nicoll D, Detmer W. Current medical diagnosis & treatment. Basic Principles of Diagnostic Test Use and Interpretation. 36th ed. Stamford (CT): Appleton & Lange; 1997.
[102] Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci

2001;38(4):263–355. doi:10.1080/20014091084227, PMID:11563810.
[103] Meister A. The gamma-glutamyl cycle. Diseases associated with specific enzyme deficiencies. Ann Intern Med 1974;81(2):247–253. doi:10.7326/0003-4819-81-2-247, PMID:4152527.
[104] Raulf M, Stüning M, König W. Metabolism of leukotrienes by L-gamma-glutamyl-transpeptidase and dipeptidase from human polymorphonuclear granulocytes. Immunology 1985;55(1):135–147. PMID:2860060.
[105] Zhao XA, Wang J, Wei J, Liu J, Chen G, Wang L, *et al*. Gamma-glutamyl Transpeptidase to Platelet Ratio Predicts Liver Injury in Hepatitis B e Antigen-negative Chronic Hepatitis B Patients With Normal Alanine Aminotransferase. J Clin Transl Hepatol 2022;10(2):247–253. doi:10.14218/JCTH.2021.00151, PMID:35528978.
[106] Kajiwara E, Akagi K, Tsuji H, Murai K, Fujishima M. Low activity of gamma-glutamyl transpeptidase in serum of acute intrahepatic cholestasis. Enzyme 1991;45(1-2):39–46. doi:10.1159/000468863, PMID:1687217.
[107] Elisaf M. Effects of fibrates on serum metabolic parameters. Curr Med Res Opin 2002;18(5):269–276. doi:10.1185/030079902125000516, PMID:12240789.
[108] Nagini S, Nagarajan B. Hypolipidemic drug clofibrate induces hepatic dedifferentiation. Biochem Int 1988;16(1):127–135. PMID:2895650.
[109] SteinmetzJ GE, Notter D. Pharmacological effects due to hypolipidemic drugs. Drug Effects on Laboratory Test Results. Berlin, Germany: Springer295–303; 1980.
[110] Gerbracht U, Bursch W, Kraus P, Putz B, Reinacher M, Timmermann-Trosiener I, *et al*. Effects of hypolipidemic drugs nafenopin and clofibrate on phenotypic expression and cell death (apoptosis) in altered foci of rat liver. Carcinogenesis 1990;11(4):617–624. doi:10.1093/carcin/11.4.617, PMID:1691053.
[111] Antonenkov VD, Gusev VA, Panchenko LF. Effect of clofibrate treatment on glutathione content and the activity of the enzymes related to peroxide metabolism in rat liver and heart. Int J Biochem 1987;19(2):187–192. doi:10.1016/0020-711x(87)90330-2, PMID:3569647.
[112] Zaidi M. Skeletal remodeling in health and disease. Nat Med 2007;13(7):791–801. doi:10.1038/nm1593, PMID:17618270.
[113] Herbeth B, Bagrel A, Dalo B, Siest G, Leclerc J, Rauber G. Influence of oral contraceptives of differing dosages on alpha-1-antitrypsin, gamma-glutamyltransferase and alkaline phosphatase. Clin Chim Acta 1981;112(3):293–299. doi:10.1016/0009-8981(81)90452-6, PMID:6113070.
[114] Choi HS, Kim KJ, Rhee Y, Lim SK. Serum γ-Glutamyl Transferase Is Inversely Associated with Bone Mineral Density Independently of Alcohol Consumption. Endocrinol Metab (Seoul) 2016;31(1):64–71. doi:10.3803/EnM.2016.31.1.64, PMID:26676328.
[115] Zhang H, Forman HJ, Choi J. Gamma-glutamyl transpeptidase in glutathione biosynthesis. Methods Enzymol 2005;401:468–483. doi:10.1016/S0076-6879(05)01028-1, PMID:16399403.
[116] Niida S, Kawahara M, Ishizuka Y, Ikeda Y, Kondo T, Hibi T, *et al*. Gamma-glutamyltranspeptidase stimulates receptor activator of nuclear factor-kappaB ligand expression independent of its enzymatic activity and serves as a pathological bone-resorbing factor. J Biol Chem 2004;279(7):5752–5756. doi:10.1074/jbc.M311905200, PMID:14634009.
[117] Hiramatsu K, Asaba Y, Takeshita S, Nimura Y, Tatsumi S, Katagiri N, *et al*. Overexpression of gamma-glutamyltransferase in transgenic mice accelerates bone resorption and causes osteoporosis. Endocrinology 2007;148(6):2708–2715. doi:10.1210/en.2007-0215, PMID:17363454.
[118] Levasseur R, Barrios R, Elefteriou F, Glass DA 2nd, Lieberman MW, Karsenty G. Reversible skeletal abnormalities in gamma-glutamyl transpeptidase-deficient mice. Endocrinology 2003;144(7):2761–2764. doi:10.1210/en.2002-0071, PMID:12810527.
[119] Asaba Y, Hiramatsu K, Matsui Y, Harada A, Nimura Y, Katagiri N, *et al*. Urinary gamma-glutamyltransferase (GGT) as a potential marker of bone resorption. Bone 2006;39(6):1276–1282. doi:10.1016/j.bone.2006.06.029, PMID:16942925.
[120] Paglia DE, Valentine WN, Dahlgren JG. Effects of low-level lead exposure on pyrimidine 5′-nucleotidase and other erythrocyte enzymes. Possible role of pyrimidine 5′-nucleotidase in the pathogenesis of lead-induced anemia. J Clin Invest 1975;56(5):1164–1169. doi:10.1172/JCI108192, PMID:1184742.
[121] Paglia DE, Renner SW, Bhambhani K. Differential effects of low-level lead exposure on the natural isozymes of erythrocyte 5′-nucleotidase. Clin Biochem 1999;32(3):193–199. doi:10.1016/s0009-9120(99)00003-x, PMID:10383080.
[122] Rees DC, Duley JA, Marinaki AM. Pyrimidine 5′ nucleotidase deficiency. Br J Haematol 2003;120(3):375–383. doi:10.1046/j.1365-2141.2003.03980.x, PMID:12580951.
[123] Wang T, Tu Y, Wang K, Gong S, Zhang G, Zhang Y, *et al*. Associations of blood lead levels with multiple genotoxic biomarkers among workers in China: A population-based study. Environ Pollut 2020;273:116181. doi:10.1016/j.envpol.2020.116181, PMID:33508628.
[124] Rygiel CA, Goodrich JM, Solano-González M, Mercado-García A, Hu H, Téllez-Rojo MM, *et al*. Prenatal Lead (Pb) Exposure and Peripheral Blood DNA Methylation (5mC) and Hydroxymethylation (5hmC) in Mexican Adolescents from the ELEMENT Birth Cohort. Environ Health Perspect 2021;129(6):67002. doi:10.1289/EHP8507, PMID:34152198.
[125] Jacobasch G, Rapoport SM. Hemolytic anemias due to erythrocyte enzyme deficiencies. Mol Aspects Med 1996;17(2):143–170. doi:10.1016/0098-2997(96)88345-2, PMID:8813716.
[126] Netzloff ML. Clinical consequences of enzyme deficiencies in the erythrocyte. Ann Clin Lab Sci 1980;10(5):414–424. PMID:4263485.
[127] Staal G, Rijksen G. Regulation of pyruvate kinase in normal and pathological conditions. Regulation of Carbohydrate Metabolism 1st ed. England, UK: Routledge; 1985.