Alcohol and it’s Effects on Micronutrient Metabolism

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When alcohol is consumed it passes through all parts of the gastrointestinal (GI) tract, liver and pancreas. Moderate intake of alcohol does not usually lead to long lasting nutritional deficiencies related to decreased absorption, digestion and metabolism of macro and micronutrients. However, excessive and chronic alcohol intake can negatively impact a person’s nutritional integrity and cause severe malnutrition as well as damage to the GI tract and accessory organs; resulting in malnutrition, disease and death. This purpose of this paper is to explain the digestion of alcohol and the nutrition complications it causes while focusing specifically on thiamin, zinc and vitamin D. A complete explanation of alcohol’s effect on all vitamins and minerals can be understood by focusing on the water-soluble vitamin Thiamin, fat-soluble vitamin D, and the mineral zinc.

Alcoholic beverages contain alcohol, carbohydrates and insignificant amounts of vitamins and minerals. Beer contains B vitamins and wine can contain iron, potassium, copper, and sodium in small trace amounts. Alcohol is the second highest source of energy of all of the micronutrients providing 7 kcal/g. Moderate drinking is defined as consumption of one drink a day for women and two drinks a day for men. Excessive and chronic drinking are defined as consumption of more than one drink a day for women equaling more than seven drinks a week, and more than two drinks a day for men equaling more than 14 drinks a week.

Alcohol is a water-soluble molecule and is absorbed throughout the GI tract by simple diffusion. 20% of alcohol consumed is absorbed through the stomach and 80% is absorbed through the small intestine. Alcohol is distributed through the body by diffusion and then through the blood into organs. It diffuses more rapidly into organs with large blood supply, such
as the lungs. The liver receives the largest amount of alcohol because it receives blood directly from the stomach and small intestine through the hepatic portal vein. The liver is the primary site of alcohol metabolism; other sites include metabolization in the stomach by alcohol dehydrogenases and excretion in urine, sweat, and breath. The liver can oxidize one ounce of alcohol in an hour. Below shows the process of alcohol metabolism in the liver.

Alcohol is oxidized to acetaldehyde by alcohol dehydrogenase. Acetaldehyde is then oxidized to acetate by acetaldehyde dehydrogenase. With the addition of Co-A, acetate is then formed into Acetyl Co-A. In each conversion, niacin in the form of NAD is used and NADH is produced. The amount of NADH produced will increase as consumption of alcohol increases. The excessive build up of NADH will degrade by two mechanisms. Route one converts pyruvate Secondary malnutrition results from poor digestion, absorption and metabolism of nutrients due to damage of the GI tract and accessory organs. Excessive alcohol intake can damage many organs and tissues. Injury to the gastrointestinal tract interferes with absorption and digestion, damage to the pancreas interferes with digestion of fats and proteins, liver damage reduces vitamin storage and increases losses by excretion, and damage to membranes inhibits the transport of various nutrients into lactate (acid), resulting in NADH converted back to NAD.
Lactate can enter the Cori cycle to produce glucose. Route two converts NADH to NAD when the malate dehydrogenase enzyme converts oxaloacetate to malate in the opposite direction of the TCA cycle. This causes malate to be produced in excess. The malate enzymes will be used to convert excess malate to pyruvate, which results in excess NADPH. The NADPH drives fatty acid synthesis. To get rid of excess NADPH, acetyl Co-A must be converted to into malonyl Co-A which will eventually get broken down through a series of steps into palmitic acid. Palmitic acid is a 16-carbon fatty acid, resulting in the conversion of NADPH to NADP. Increase in palmitic acid results in a fatty liver and excessive fat storage throughout the body.

While studies have shown that consuming alcohol in moderation does not largely interfere with absorption and metabolism of nutrients, alcohol consumed in excess can cause nutrient deficiencies through primary or secondary malnutrition. Primary malnutrition is the result of substituting food calories with alcohol calories. Increased alcohol consumption can cause an individual to not receive proper nutrition because of increased consumption of empty calories, loss of appetite, and an increase of alcohol-related expenses may result in decreased funds available for food. Several examples of the damage caused by alcohol include damage to the oral cavity resulting in inflammation of the tongue, tooth decay, gum disease, impaired esophageal motility, and weakened esophageal sphincter. The damage to the oral cavity can make it difficult and painful for a person to chew and swallow. Chronic use can cause gastric bleeding and shrinkage of the gastric mucosa. This results in pain when eating and a defect in vitamin and mineral digestion. Decreased gastric secretions results in a low pH. Vitamins such as B12, zinc, calcium, iron, magnesium and chromium need a high pH to begin the digestive process. Without the high pH of the stomach, the initial stages of breakdown will not occur and
the vitamins and minerals will not be able to transition to the form needed to be absorbed and utilized by the body. In the small intestine alcohol competes with vitamins and minerals for absorption. Specifically, in the jejunum the alcohol concentration can drop from 10% to 1.45% over a distance of just 30 centimeters (Bode, 1997). Heavy drinking can result in heavy bleeding and damage to duodenum. As alcohol enters the intestine from the stomach, the duodenum is the first segment of the intestine to be exposed causing excessive damage. Damage to the duodenum would interfere with its ability to absorb nutrients.

Alcohol liver disease and Pancreatitis are diseases that can occur from excessive alcohol intake. A study on rats and excessive alcohol intake shows that when their livers are flooded with large amounts of alcohol a release of vitamin stores occurs from liver cells except for trace amounts of biotin, Vitamin C, Vitamin E, and β-carotene (Bode, 1997). This indicates that one night of heavy drinking can deplete vitamin and mineral stores in the liver cells. Chronic alcohol intake can result in fatty liver and eventually lead to cirrhosis. The deposits of fat and damaged cells causes decreased stores of vitamins and glycogen and impairs output of bile from the liver, resulting in an impairment of fat-soluble vitamin absorption. Inflammation and damage to the pancreatic cells in acute pancreatitis and chronic pancreatitis causes decreased output of enzymes needed for vitamin, mineral, fat, carbohydrate and protein metabolism. These results have lead to a theory called the stone theory. It is thought that the inflamed and damaged pancreatic cells harden and form stones that block the ducts that release the pancreatic enzymes (Vonlaufen, 2007).

To gain a clearer understanding of alcohol's effect on micronutrients; thiamin, vitamin D, and zinc will be discussed in detail.
Thiamin

Research shows that Thiamin from animal products occurs in the phosphorylated form and must be digested prior to absorption by intestinal phosphatases produced by the acinar exocrine cells of the pancreas (Gropper, 2013). After Thiamin has been digested into free Thiamin both the intestinal absorption at the jejunum and ileum, as well as transport across the basolateral membrane into the blood, are accomplished by the active transporter proteins ThTr1 and ThTr2 (Gropper, 2013). To our knowledge, chronic consumption of alcohol results in Thiamin deficiency as a direct result of its effect on the enterocyte pancreatic acinar cells (Subramanya, 2010).

Chronic alcohol consumption prevents absorption of Thiamin from the lumen into the enterocyte across the brush border membrane (BBM) and transportation of Thiamin from the enterocyte into the blood across the basolateral membrane (BLM) (Subramanya, 2011). The carrier-mediated transport protein THTR1 is present at both the BBM and the BLM while the transporter protein THTR2 is only present at the BBM (Gropper, 2013). Within the enterocyte chronic alcohol exposure caused a significant inhibition of the genetic expression of both THTR1 and THTR2 at the mRNA and at the transcription levels (Subramanya, 2010). The decrease in available transport proteins caused a systemic thiamin deficiency.

Thiamin produced by normal microflora in the large intestine is absorbed through a carrier-mediated transport mechanism (Subramanya, 2010). While alcohol is primarily metabolized in the stomach and small intestine, it is assumed that the large intestine is exposed to alcohol from the blood side instead of the lumen side. As a result of this alcohol exposure the transporter proteins are also not expressed at the mRNA and transcription level due to alcohol
exposure (Subramanya, 2010).

Thiamin is important for pancreatic function because it is used by the pancreas as a coenzyme in energy metabolism. Free thiamin is converted to the active form thiamin pyrophosphate (TPP) inside the cytoplasm and the mitochondria of pancreatic cells via the enzyme thiamin pyrophosphokinase (Gropper, 2013). Current evidence shows that the ability of the pancreatic acinar cells to uptake thiamin and use the available thiamin was decreased by chronic alcohol exposure in two ways. First, a decrease in the thiamin metabolizing enzymes thiamin pyrophosphokinase and thiamin pyrophosphatase resulted in a decreased ability of the pancreatic acinar cells to both activate free thiamin to TPP, as well as a decreased ability to cleave TPP for use by cells. Second, a decrease in the expression of the mitochondrial TPP transporter resulted in a decreased ability of the pancreatic acinar cells to use TPP as a coenzyme for metabolic reactions within the mitochondria leading to a decrease in available cellular energy. (Subramanya, 2011)

It should be noted that the effects of chronic alcohol consumption are quite different than the effects of moderate alcohol consumption on thiamin status. A small study showed that moderate alcohol consumption of 60g of ethanol, or approximately four beers spread over the course of a day for several months did not have a significant effect on thiamin status (Wood, 1982).

In conclusion of thiamin, it has been shown that chronic alcohol consumption decreased the expression of the intestinal transport proteins ThTr1 and ThTr2 at the mRNA and the transcription levels, inhibited uptake of thiamin by pancreatic acinar cells, decreased expression of the mitochondrial TPP transporter, as well as the expression of both the enzymes thiamin
pyrophosphokinase and thiamin pyrophosphatase. While the exact mechanisms by which these effects occur remain unknown, the damaging effects of chronic alcohol consumption are clear.

**Zinc**

Zinc is an essential trace mineral found in the body in amounts between 1.5-3.0 g. It is found in all organs and is almost always found as the divalent ion (Zn2+) in the human body. In food zinc is found complexed with nucleic acids and with amino acids as part of peptides (Gropper & Smith 2013). Once ingested, zinc must be hydrolyzed from the amino acids and nucleic acids before absorption begin to can occur. Hydrolyzation occurs because of the acidic environment of the stomach. Zinc then moves into the upper GI tract where most of its absorption will occur. Zinc crosses into the enterocyte by carrier-mediated transport and also by diffusion (Gropper & Smith 2013).

The carrier-mediated transport system is the main means of zinc absorption into the enterocyte. This system uses the transport protein ZIP4 to bind with zinc across the border and into the enterocyte. This system is saturable and will reach a limit. It can generally uptake 7-9 mg of zinc each day. When an excess amount of zinc is in the transport system, diffusion of zinc between cells will increase as a means to increase absorption (Gropper & Smith 2013). Once in the cell zinc can be stored as part of vesicles, the trans-golgi network, or in the main form of storage as part of metallothionein. Zinc can also be transported across the basolateral membrane by ZnT1 into venous circulation, and can be transported by several different transport proteins including albumin, transferrin, immunoglobulin G, and low-molecular weight binding proteins. (Gropper & Smith 2013).
Intake of alcohol, especially excessive intake, has been seen to impair the status of many micronutrients and zinc is not an exception. As previously discussed, the main reason for alcohol-related zinc deficiency is observed in individuals who consume alcohol and simultaneously consume a lower intake of food. Alcoholics often consume 50% of their daily calories from alcohol. Some research even suggests that up to 90% of alcoholics are not consuming enough zinc in their diets (Watson & Watzl 1992).

Another explanation of how alcohol will cause deficiency of zinc involves zinc absorption and storage. When zinc enters the enterocyte it can be stored as part of a metallothionein storage or transported into venous circulation to be transported and used. Alcohol has been shown to disrupt metallothionein storage and decrease its availability. This should mean that more zinc would enter the blood and levels would actually decrease, but this is not the case. One proposed mechanism to explain this is that stress hormones can increase metallothionein activity and as a result, storage of zinc will increase. High amounts of stress
hormones are often seen in alcoholics (Watson & Watzl 1992).

Lastly, a reason as to why zinc deficiency can occur with increased alcohol consumption has to do with cytokine activity. Cytokines are proteins that play a large role in cellular communication and activity. Alcohol intake may lead to an increase in cytokine activity, which in turn will have extreme effects on many biochemical processes occurring in the body. One of these effects is the decrease of albumin production. Albumin is one of the transport proteins in the blood that will carry zinc. This decrease will lower the body’s ability to use zinc in an efficient way (Watson & Watzl 1992).

A human research study evaluated the effects of alcohol on zinc levels in the body. This study used otherwise healthy alcoholics as its subjects and measured their levels of zinc in the body. The findings showed normal serum zinc levels, but also showed that the subjects had alveolar macrophage intracellular zinc levels that were extremely decreased. These findings provide enough evidence to show that chronic alcohol use can cause a deficiency of zinc in the human body; especially in the lungs, and have adverse effects on the immune system. In this situation supplementation of zinc would be beneficial in reversing the deficient state (Ashish 2013).

**Vitamin D**

A major source of vitamin D₃ is made in the form of cholesterol metabolite, 7-dehydrocholesterol, in the skin as a result from sunlight exposure. The cholesterol is uniform throughout the epidermis and dermis where the conversion of previtamin D₃ takes place under a heat-dependent process. Only a small proportion of foods provide a dietary source of vitamin D₃ such as fatty fish, eggs, cheeses, mushrooms, supplements, and artificially fortified foods.
Dietary-derived vitamins are in the forms of ergocalciferol D$_2$ and cholecalciferol D$_3$. These are incorporated into micelles in the intestinal lumen, then are transported by chylomicrons into circulating blood. Vitamin D from both skin synthesis and dietary sources either store the vitamin in adipose tissue and muscle from the chylomicrons or the chylomicron remnants deliver the remainder to the liver to undergo 25-hydroxylation (Kitson, 2012).

Vitamin D reaching the liver undergoes a process by cytochrome p-450 hydroxylases to begin the generation of vitamin D’s active form. In the liver, 25-hydroxylase, which is NADPH-dependent, function in the mitochondria to have CYP2R1 and CYP27A1 enzymes hydroxylate vitamin D to form 25-(OH)D, or calcidiol. The majority of serum 25(OH)D, about 88%, is bound to vitamin D-binding protein (DBP) and is released into the blood (Kitson, 2012). Circulating 25-(OH)D concentrations reflects vitamin D status, which is generally thought to be sufficient if between 30 and 40 ng/ml (Gropper, 2013).

The final reaction in the synthesis of vitamin D is 1α-hydroxylation. This is taken up by the kidneys in response to increased concentration of parathyroid hormone (PTH) and fibroblast-like growth factor 23. The 25-(OH)D-DBP complex binds to the kidney’s cubilin-megalin plasma membrane receptor to form a megalin-DBP-25-(OH)D complex (Gropper, 2013). Specifically, it is mediated by an NADPH-dependent mitochondrial enzyme 1α-hydroxylase (CYP27B1) that produces the active form 1α,25-dihydroxyvitamin D or calcitriol (Kitson, 2012). Concentrations of 1α,25(OH)$_2$D influences the enzyme 1-hydroxylase to activate the vitamin D receptor (VDR). VDRs usually exists as heterodimer with the retinoid X receptor and are associated with DNA sequence as a transcription factor that binds to vitamin D response elements in the promoter region of target genes. Calcitriol mechanisms of action
effects several body processes that influence calcium and bone homeostasis. Other roles of calcitriol include cell proliferation, differentiation, and growth, as well as immunomodulation and angiogenesis (Kitson, 2012).

Calcitriol synthesis is stimulated by changes to calcium concentration and release of PTH. Low serum calcium concentrations known as hypocalcemia, stimulate the synthesis of PTH and 1-hydroxylase, thus the synthesis of calcitriol. This increases calcium reabsorption in the kidneys and stimulates metabolism of bone. In turn, when calcium concentrations are high due to increased vitamin D concentration, PTH release is inhibited and 24-hydroxylase in the kidneys is stimulated to produce 24,25(OH)₂, or cholecalciferol. Also, calcitriol decreases the transcription gene of PTH synthesis. In addition, calcitonin is released to block calcium and phosphorus mobilization from bones by inhibiting osteoclast activity. Calcitonin plays another role by inhibiting tubular reabsorption of the kidney’s calcium and phosphorus, leading to increased urinary calcium excretion. When high calcium concentration are present, it has been found to promote anabolism and mineralization (Gropper, 2013).

In a current study, total bone mineral density reduced as alcohol consumption increased as the consequence to hypocalcemia. Higher serum levels of inactive vitamin D, calcidiol, in alcohol abusers may indicate disturbed vitamin D metabolism to activate calcitriol. Risk factors include osteoporosis in both men and women as a result of inhibition of osteoblastogenesis and stimulation of osteoclast differentiation and activation (Shanker, 2008). Other health claims include chronic liver disease and chronic hepatitis C (CHC). Those with liver
disease have a concentration of 25(OH)D and 1α25(OH)2D deficiency is 84% and 77%, with a decrease in DBP levels. Vitamin D status also showed reports associated with CHC. At a cellular level, vitamin D deficiency is due to the decrease of CYP27A1 enzyme in the liver. This related that patients with CHC have an increase of hepatic necroinflammation activity. The study also demonstrated that DBP levels are significantly lower with CHC patients who developed advance fibrosis. The vitamin D active mechanisms that caused anti-inflammatory and immune modulatory properties showed an impact on disease progression such as CHC (Kitson, 2012).

While excessive alcohol consumption can lead to malnutrition, disease and death, there are studies that show there are some health benefits to alcohol when consumed in moderation. Drinking in moderation at dinner can improve digestion since alcohol raises the pH level of the gastric juices, resulting in better digestion of many vitamins and minerals. Drinking in moderation can decrease cardiovascular disease. This is done because alcohol raises HDL, the good cholesterol, and prevents blood clots that may occur in the arteries of the heart. Studies have shown a 30-40% decreased risk of type 2 diabetes in moderate drinkers consuming 1-3 drinks a day. The risk rises at 4 drinks a day. This may be due to alcohol's role on increasing sensitivity to insulin. Moderate alcohol consumption has shown a decrease in gallstones. Moderate alcohol also decreases the risk of death from all diseases states. In a literature review, a Harvard study found a 21-28% decreased risk of death in men. A study from China showed a 20% decrease in death in middle-aged men. A British 13-year study consisting of 12,000 men found reduced risk of death from all disease states including cancer, diabetes, cardiovascular diseases, and stroke. An Italian study consisting of 1,536 men ranging in ages of 45-65 found
that two years of life was gained in moderate drinkers vs. nondrinkers (Watson, 1992). While one will want to avoid excessive and chronic alcohol consumption to avoid diseases and malnutrition, alcohol in moderation in healthy individuals appears to be ok and beneficial.

It is clear that alcohol can lead to malnutrition by interfering with absorption, digestion and metabolism of macro and micronutrients. However, studies suggest that the main contributor to malnutrition is through primary malnutrition. Studies have shown that malnutrition is not common in alcoholics who are wealthy and middle class (Watson 1992). Severe malnutrition seems to appear only in the lower class and homeless communities. This indicates that money being spent on alcohol instead of food is a large contributor to malnutrition in alcoholics.

Conclusion

Many of the mechanisms for how alcohol damages the GI tract are not known. Further research on the actual cause of damage to the GI tract could bring further insight to the how alcohol affects nutrition. Although recent studies have demonstrated that chronic ethanol use is an accurate biomaker for serum $1,25(OH)_2D_3$ levels, further studies for long-term association between chronic alcohol consumption and low vitamin $D_3$ levels is needed. Studies have been done to provide evidence about alcohol's role in zinc deficiency, but more research is needed to provide enough evidence to determine the exact mechanism. More research is being done concerning alcohol's role in metallothionein storage and how that changes zinc levels in the body.
References


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