



Vitamins and Supplements in TBI

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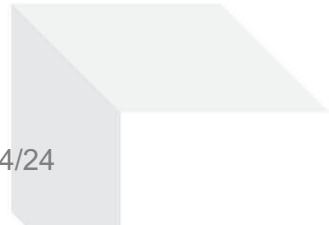
Disclosure

- No Disclosure

At the end, participants should be able to:

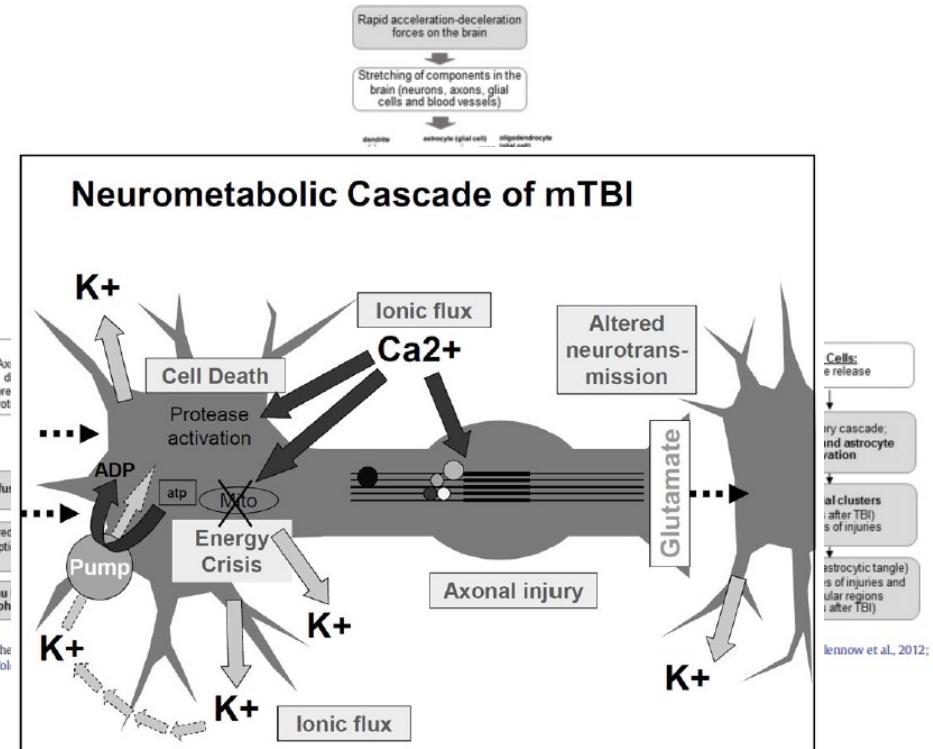
- Identify current evidence and clinical practice guidelines on the supplementation of minerals and vitamins for Traumatic Brain Injury.
- Implement appropriate guidelines for vitamin and mineral supplementation for acute Traumatic Brain Injury
- Identify vitamin and mineral deficiencies, such as Wernicke's Encephalopathy, to prevent and treat these clinical entities.

Vitamins



Traumatic Brain Injury (TBI)^{1,2,3}

- TBI: every injury is unique
 - Focal Contusions
 - Diffuse Axonal Injury
- Damage to neurons leads to ion flux and massive glutamate release
 - Leads to an Energy Crisis
 - Increased demand for ATP



From: Giza & Hovda, *Neurosurgery*, 2014, 75(04):S24-S33

Vitamins and Minerals

- These are micronutrients that are required for normal function and are not produced in our bodies.
- Vitamins: organic substances
 - Fat Soluble: Vitamin A, D, E, K
 - Water Soluble: Vitamin C, B vitamins
- Minerals: inorganic elements
 - Calcium, sodium, potassium
 - Trace minerals: copper, magnesium, and zinc
- Essential Fatty Acids/Essential Amino Acids
 - These are other molecules needed for dietary consumption, but will not be covered today
- Recommended daily intake
 - Developed by the National Academy of Medicine
 - [Vitamins and Minerals | The Nutrition Source | Harvard T.H. Chan School of Public Health](https://www.hsph.harvard.edu/nutritionsource/vitamins-and-minerals/)



From: <https://smpnutra.com/what-are-vitamins-the-history-benefits-future-predictions>

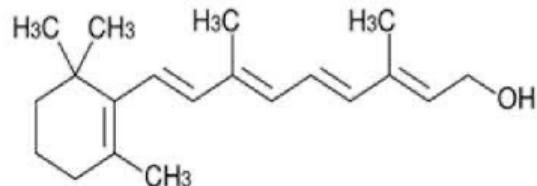
Vitamins

- Vitamin Deficiencies have been described since Ancient Egyptians
- Currently described 13 Vitamins
 - Most Vitamins are groups of associated molecules called Vitamers
 - Multiple molecules previously thought to be vitamins have been reclassified
 - Choline is occasionally listed as a vitamin
- Essential Fatty Acids are not Vitamins. Only 2 needed for humans:
 - Linoleic Acid (Omega-6 fatty acid)
 - Alpha-linolenic acid (Omega-3 fatty Acid)
- Essential Amino Acids are not Vitamins
 - 9 Amino acids must be gained through diet

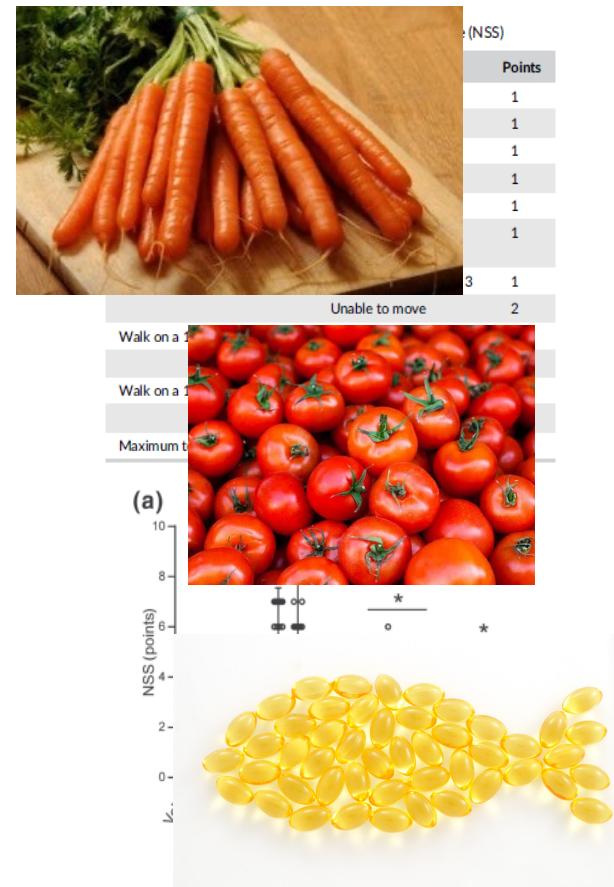
Previous	Vitamin and Year of Discovery	Change [76]
Vitamin B ₁	Vitamin A (retinol)	1913 nd in body
Vitamin B ₈	Vitamin B1 (Thiamine)	1910 nd in body
Vitamin B ₁₀	Vitamin B2 (Riboflavin)	1920 does min).
Vitamin F	Vitamin B3 (niacin)	1936
Vitamin G	Vitamin B5 (Panthotenic Acid)	1913
Vitamin H	Vitamin B6 (Pyridoxine)	1934
Vitamin J	Vitamin B7 (Biotin)	1936 n reclassified
Vitamin L ₁	Vitamin B9 (Folate)	1941
Vitamin L ₂	Vitamin B12 (cobalamin)	1948 d in body
Vitamin M	Vitamin C (Ascorbic Acid)	1920 en essential
Vitamin P	Vitamin D (Calciferol)	1920
Vitamin Pl	Vitamin E (Tocopherol)	1922
Vitamin U	Vitamin K (Phylloquinone)	1929 ized in body

From: <https://en.wikipedia.org/wiki/Vitamin>

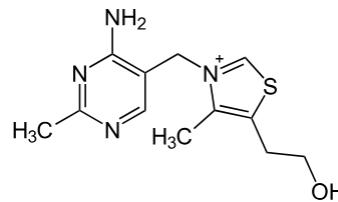
Vitamin A



- Forms of Vitamin A:
 - Preformed Vit A: Retinol, retinyl esters
 - Provitamin A: alpha-carotene/beta-carotene
 - Converted to retinol
- Vitamin A helps to regulate cell growth, maintain health endothelial cells, bone remodeling
 - Vitamin A Deficiency: Night blindness, xerophthalmia, dry skin/hair
 - Vitamin A Toxicity: Bone pain, N/V, Blurry vision/photophobia
 - Increased risk of lung CA in smokers with Vit A high dose supplements
- Brain Injury:
 - Vitamin A aids in neuron development and maintenance of neural plasticity
 - Limited Studies. Murine study showed supplementation of Vit A metabolite improved neurological recovery, but not statistically significant



Vitamin B1 (Thiamine)

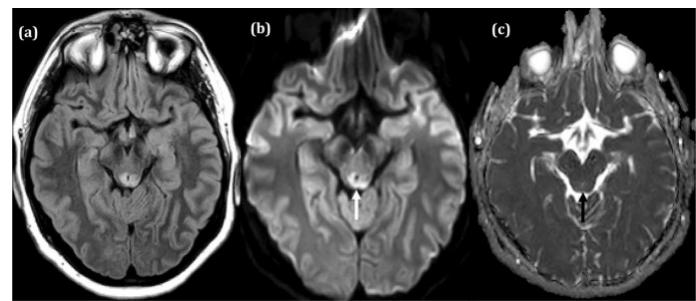


- Important cofactor in multiple reactions
 - Only a small amount is stored in the liver, so must be ingested regularly
 - Found in Green Peas, Beans, Yogurt, Sunflower Seeds
- RDI is 1.2 mg/day for men and 1.1 mg/day for women
 - People can tolerate up to 1500-8000 mg daily
 - Toxicity: no established toxic level
 - 1 case report from 1941: taking 10,000 milligrams a day
- Deficiency:
 - Wet Beriberi: cardiomyopathy
 - Dry Beriberi: peripheral neuropathy
 - Gastrointestinal Beriberi: abdominal pain or vomiting
 - Wernicke Encephalopathy



Thiamine and Brain Injury

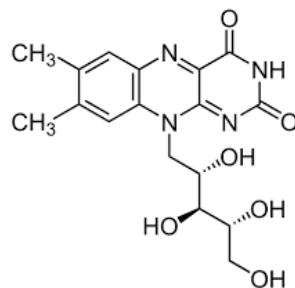
- Murine Model: improved memory after TBI
 - Immediate admin decreases iNOS and TNF-R1
 - May help to decrease mitochondrial stress after TBI
- Wernicke Encephalopathy
 - No published incidence with TBI but most likely is very high
 - Often undiagnosed, MRI only 50% sensitive
 - EFNS Diagnostic criteria (2 of the following):
 - Nutritional deficiency
 - Ocular symptoms
 - Ataxia
 - Mental Status Changes
 - Recommend early initiation of high dose thiamine when suspected
 - **500 mg IV q8 hr for 3-8 days, then consider high dose orally, 500 mg BID**



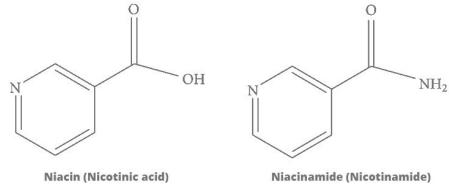
From: Ota et al, 2020. *Jpn J Radiol*

Vitamin B2 (Riboflavin)

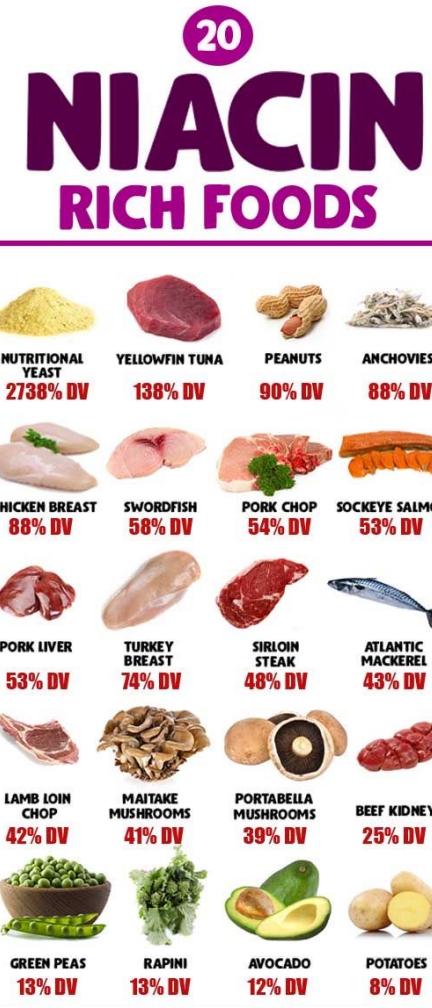
- Supplies the cofactor flavin (FAD/FMN)
 - Antioxidant: helps to regenerate glutathione
- RDI: men 1.3 mg/day, women 1.1-1.6 mg/day
 - Mostly in meat, but also in almonds/spinach
 - Deficiency: fatigue, swollen throat, blurred vision
 - Skin: angular cheilitis, hyperpigmented scrotum/vulva
 - Toxicity: A toxic level has not been observed
- Traumatic Brain Injury
 - Murine Model: reduced GFAP and edema
 - When combined with Mg helps to improve function
 - Current Trial: looking at B2 and improvement in GOAT
 - **Migraine: 400 mg daily B2 for 3 months decreases intensity/severity/duration of headache**



Vitamin B3 (Niacin)

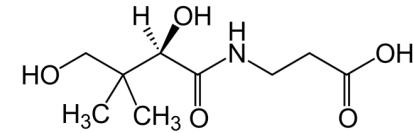


- Co-enzyme in over 400 enzymatic reactions
 - Supplies NAD/NADP in essential oxidation-reduction reactions
- Niacin is present in most foods
 - Red meats, poultry, brown rice, bananas
 - Body also converts tryptophan into Niacin
- Deficiency: Pellagra
 - Dementia: also lethargy, apathy, depression
 - Diarrhea: typically watery.
 - Dermatitis: erythematous, typically malar, with burning sensation
- Toxicity: flushing, dizziness, GI distress
 - *May also increase uric Acid levels and cause gout*
- Traumatic Brain Injury
 - Murine Model: Does not improve cognitive outcomes, does reduce reactive damage in the brain
 - Humans: trial in Pakistan completed in 2023 looking at B12 vs. B3 supplementation in Pediatric Brain Injury

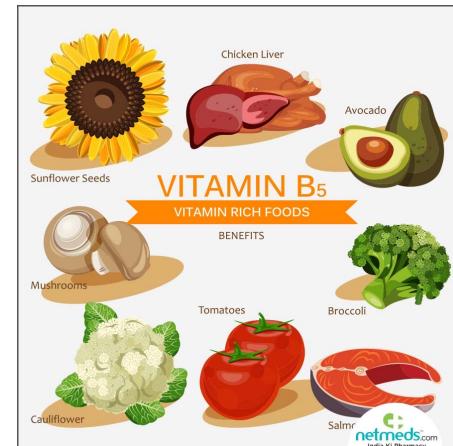


Nutrition
ADVANCE

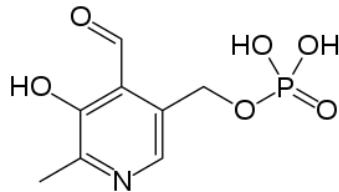
Vitamin B5 (Pantothenic Acid)



- Precursor to the synthesis of Coenzyme A
 - CoA involved in hundreds of reactions
- Vitamin B5 has been found in all living cells
 - Best sources are beef, chicken, organ meats
- Deficiency: very rare/typically seen with other vitamin deficiencies
 - Headache, fatigue, nausea, muscle cramps
- Toxicity: rare
 - Supplementation of 10 g/day can cause stomach upset/mild diarrhea
- Traumatic Brain Injury
 - Murine Model: provitamin B5 helps reduce apoptosis and oxidative damage after TBI
 - No recommendations for use in TBI



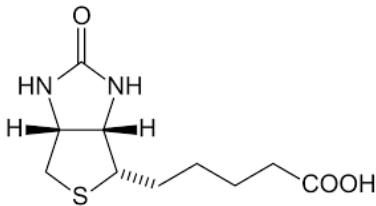
Vitamin B6 (Pyridoxine)



- Active B6 = Pyridoxal 5' Phosphate B
 - Coenzyme that assists in more than 100 enzyme reactions
 - Found in a variety of foods
 - Beef Liver, Tuna, Chickpeas
 - Deficiency: often associated with other Vitamin Deficiencies (B9, B12),
 - Microcytic anemia, depression, confusion
 - Caused by poor renal function, autoimmune, alcohol, and due to multiple drugs (anticonvulsants)
 - Toxicity: rare, can occur with supplementation of greater than 1000 mg daily
 - Ataxia, Nausea, neuropathy in hands/feet
- Traumatic Brain Injury
 - Murine: reduced cortical damage and improved functional use
 - Patients on Prolonged Levetiracetam: **can use pyridoxine 50-100 mg to help with irritability secondary to AED treatment**



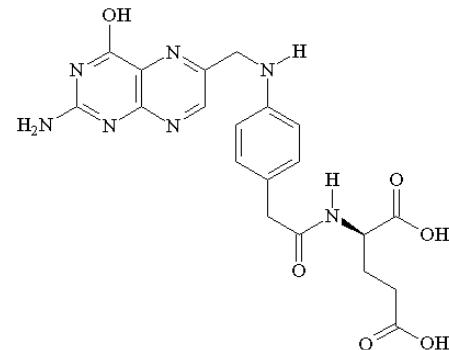
Vitamin B7 (Biotin, Vit H)



- Biotin assists in breaking down fats, carbs, and protein
 - Found in eggs, avocados, beef liver
- Rare Deficiency: secondary to errors of metabolism
 - Conjunctivitis, ataxia, seizure, developmental delay in children
 - May contribute to brittle hair syndrome
- No known toxicity
 - Often added for hair, nail, and skin supplementation
 - High supplement levels can interfere with lab tests (TSH/trop)
- Traumatic Brain Injury
 - Deficiency has been associated with impairment in neurogenesis
 - Murine Model: may be protective after irradiation



Vitamin B9 (Folate/Folic Acid)

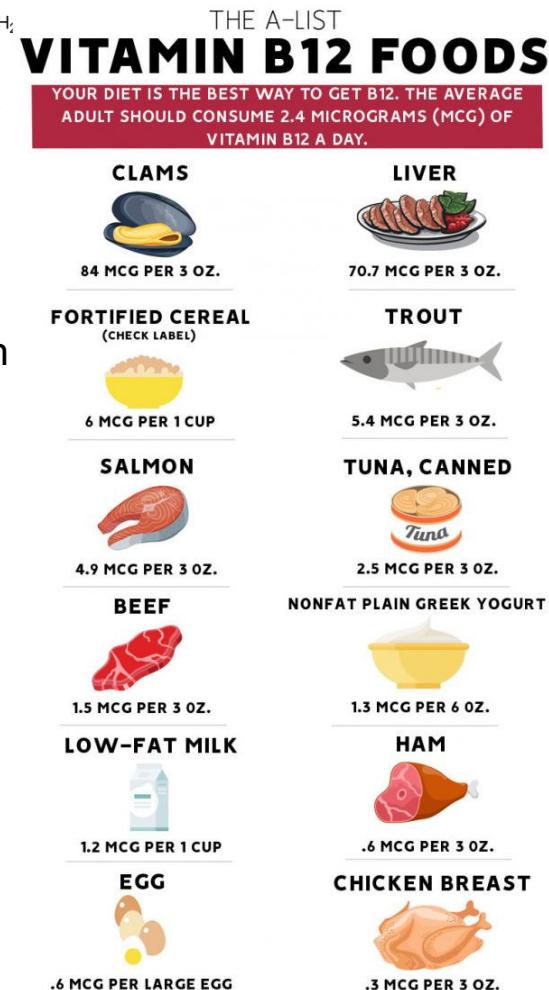
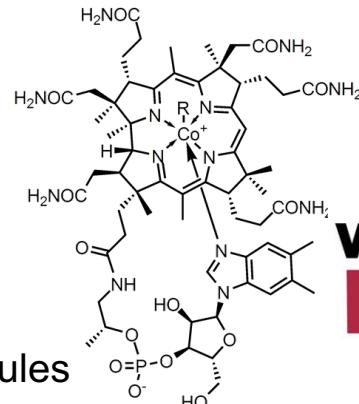


- Assists in formation of DNA/RNA
 - Key role in breaking down homocysteine
 - Needed to produce RBC and for rapid growth
 - Found in Dark green leafy vegetables, Beans, Peanuts
- Deficiency: rare due to ubiquitous sources
 - AUD, pregnancy, MTHFR variant carriers
 - Megaloblastic Anemia, Neural Tube Defects
- Toxicity: rare but can result in death
 - *High supplement use can mask B12 deficiency*
- Traumatic Brain Injury
 - Murine: high dose folate did not show any difference
 - Humans: **B9 may help reduce incidence of HAP**
 - AED (Phenytoin/Carbamazepine) can cause B9 deficits
 - consider supplementation if Homocysteine levels elevated

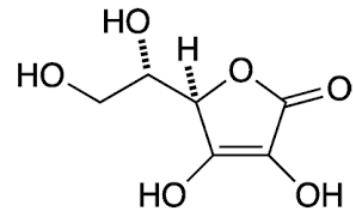


Vitamin B12 (Cobalamin)

- Found Naturally in animal foods
 - Needed to form RBC/DNA
 - May also help with stabilize of axon microtubules
- Absorption:
 - B12 is typically bound to animal protein
 - Stomach HCl unbinds the B12 where it combines with a protein called Intrinsic Factor so it can be absorbed in the small intestine
- Deficiency: up to 15% of population is deficient
 - Megaloblastic (pernicious anemia), Neuropathy, Dementia
 - Measure MMA/Homocysteine as deficiency can still have normal B12 level
- Traumatic Brain Injury:
 - Murine: may help to improve axon regeneration after TBI
 - Humans: **elevated Homocysteine level in ICU is a predictor of poorer outcome**
 - Trial in Pakistan completed in 2023 looking at B12 vs. B3 supplementation in Pediatric Brain Injury



Vitamin C (Ascorbic Acid)

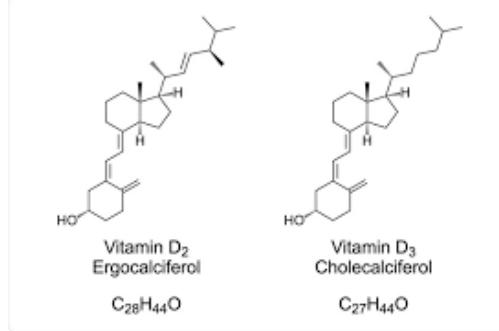


- Essential co-factor for collagen biosynthesis, carnitine and catecholamine metabolism, and iron absorption
 - Found in citrus fruits and leafy vegetables. Cooking can destroy Vitamin C
 - Need 90 mg/day for men and 75 mg/day for women
 - Smokers need more as it can deplete levels
 - Deficiency: Scurvy! Iron-deficiency anemia
 - Toxicity: possible with >3000 mg/day dosing
 - Can cause iron overload, nephrolithiasis, gout attack, diarrhea
- Traumatic Brain Injury:
 - Humans: retrospective study showed Vit C and E supplementation improved outcomes in mortality and GOS-E scores



Vitamin D (Calciferol)

- Both a nutrient and a hormone
 - Vitamin D2 (ergocalciferol): made by plants/fortified in food
 - Vitamin D3 (cholecalciferol): made by human body/animal foods
 - Critical in Ca²⁺ and PO₄⁻ absorption for bone health
- Adults need at least 600 IU/day, >70 years old need 800 IU
 - The Endocrine Society recommends 1500-2000 IU daily
 - Deficiency: rickets, fatigue, increases when N of 37th parallel
 - Toxicity: extremely rare, levels over 150 ng/mL may cause hypercalcemia, constipation, polydipsia, confusion
- Traumatic Brain Injury
 - Vitamin D deficiency is associated with poor functional outcomes at hospital discharge and 6 month mortality
 - Retrospective study showed improved outcomes in patients who got replacement in deficiency (especially with high dose, 120K IU replacement)
 - Vitamin D and Progesterone RCT 2010: improvement of severe TBI on GOS compared to placebo or progesterone alone at 3 months



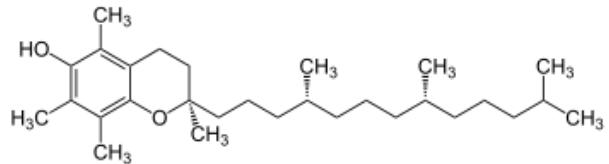
MYFOODDATA

Top 10 High Vitamin D Foods

20μg of Vitamin D = 100% of the Daily Value (%DV)

1 Fish (Salmon)	2 Crimini (Chestnut) Mushrooms (Exposed to UV Light)
142% DV (28.4μg) per 6oz fillet 265 calories	139% DV (27.8μg) per cup 19 calories
3 Fortified Milk	4 Fortified Milk Substitutes (Soy Milk)
32% DV (6.3μg) per 16oz glass 298 calories	29% DV (5.8μg) per 16oz glass 160 calories
5 Fortified Tofu	6 Fortified Yogurt
28% DV (5.7μg) per cup 208 calories	16% DV (3.2μg) per cup 250 calories
7 Fortified Breakfast Cereal	8 Fortified Orange Juice
12% DV (2.5μg) per 3/4 cup 96 calories	12% DV (2.5μg) per cup 117 calories
9 Pork Chops	10 Eggs
10% DV (2.1μg) in 1 pork chop 525 calories	6% DV (1.1μg) in 1 large egg 78 calories

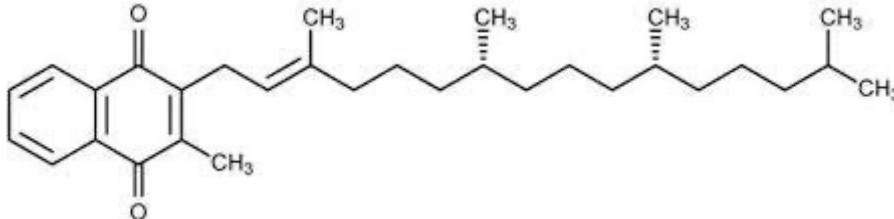
Vitamin E (alpha-tocopherol)



- Alpha-Tocopherol is the version used in humans
 - Antioxidant effects, thought to protect against dementia
 - Found in plant-based oils, nuts/seeds, fruits & veggies
 - Need approximately 22 IU (or 15 mg daily)
- Deficiency: rare, found in digestive disorders
 - Pancreatitis, CF, Celiac Disease
 - Retinopathy, Peripheral neuropathy, Ataxia
- Toxicity: associated when supplementing >1465 IU/daily
 - Causes increased risk of excess bleeding
- Traumatic Brain Injury:
 - Vitamin E deficiency associated with poor outcomes
 - Early supplementation decreased organ failure and hospital stay
 - Supplementation with Vit C demonstrated improvement in mortality
 - Vit C acts to regenerate Vitamin E so it continues to be an antioxidant



Vitamin K

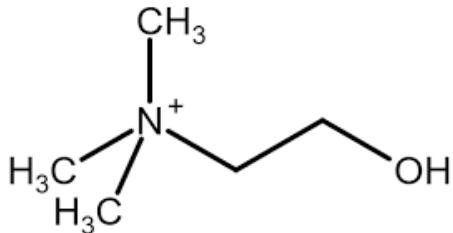


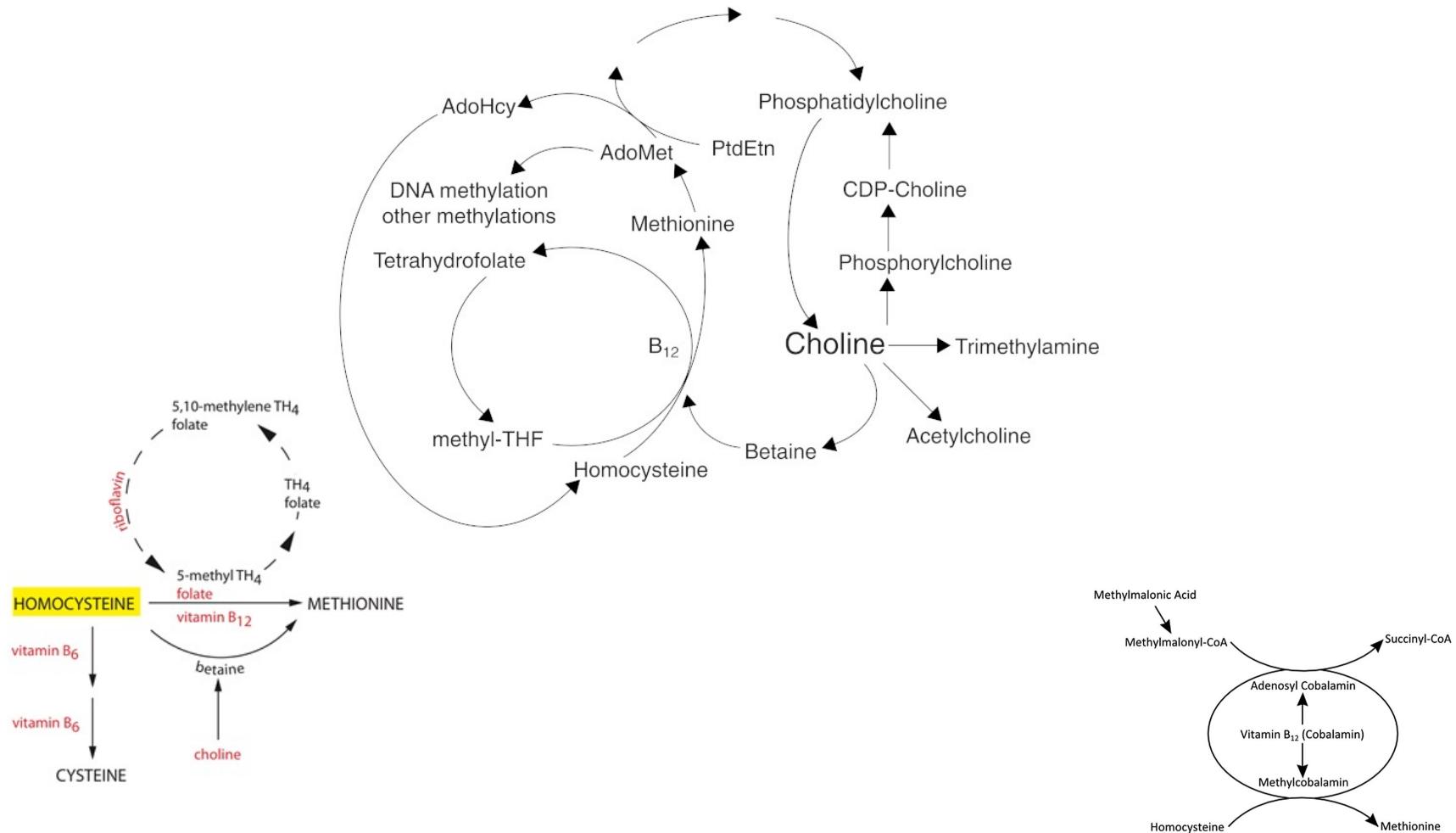
- 2 forms: phylloquinone and menaquinones
 - Leafy vegetables, soybean and canola oil
 - Makes various proteins for blood clotting and bone formation
 - Recommended to have 120 mcg/daily for men, 90 for women
- Deficiency: prolonged clotting/osteopenia/osteoporosis
- Toxicity: rare (Synthetic K3 is toxic)
 - Jaundice, hyperbilirubinemia, hemolytic anemia
- Traumatic Brain Injury:
 - Vitamin K is involved in sphingolipid metabolism, but unknown what direct effect it has in injury
 - Vitamin K is not stored in the brain
 - No specific studies evaluating supplementation in TBI



Choline

- Occasionally listed as a vitamin
 - Converted into acetylcholine
 - Also assist in breakdown of cholesterol
 - No RDA, the AI is 550 mg/day for men, 425-550 for women
 - Found in meat, fish, poultry, and mushrooms (coffee)
- Deficiency: rare, causes fatty liver and damage
- Toxicity: hypotension and liver toxicity, fishy body odor
 - Upper tolerable limit is 3.5 g/day
- Traumatic Brain Injury
 - COBRIT trial (2012): no benefit demonstrated
 - Has been shown to decrease ICU mortality in a retrospective case, however, in the US may have been removed citicoline in 2009
 - Trial of Citicoline and amantadine in Egypt (possibly ongoing)





Recommendations (Vitamins)

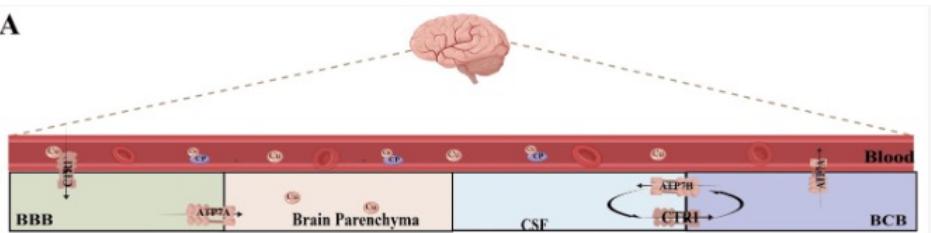
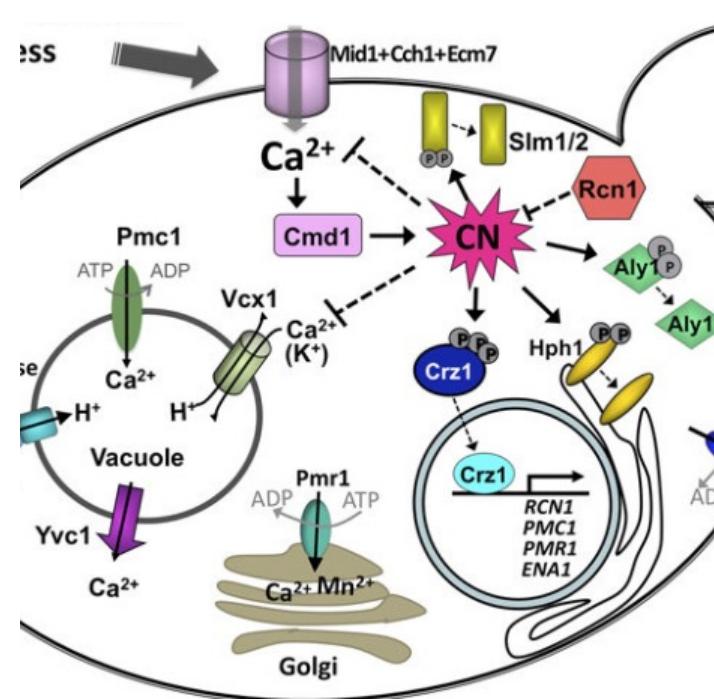
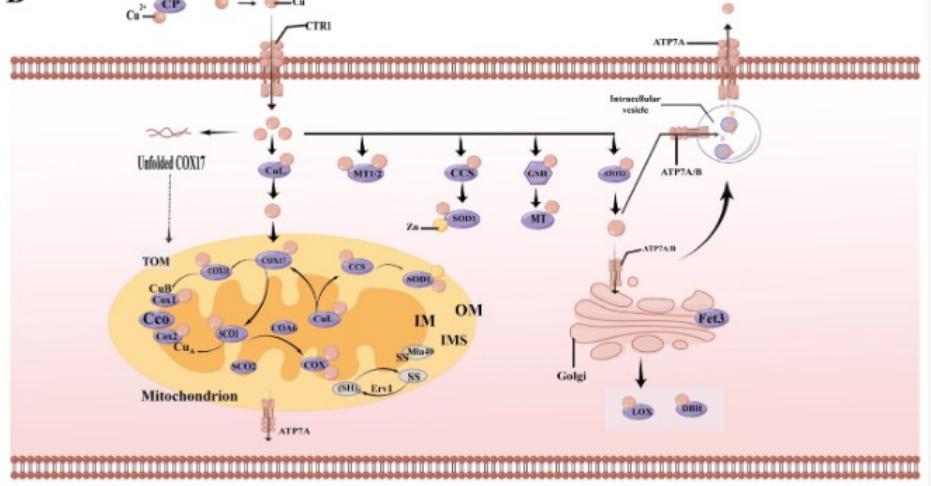
- B1 (Thiamine): have a low suspicion for WE and starting high dose thiamine
- B2 (Riboflavin): 400 mg/day for 3 months to help with PTH/migraine
- B9 (Folate): may help reduce HAP and ventilator days
- B12 (cobalamin): screen for homocysteine levels on admission
- IV Vit C/E: may help reduce ICU stay
- Vit D: screen for deficiency and replace
 - IV Progesterone and Vit D may benefit from larger prospective study
- Choline: supplementation may help, is only OTC

Mineral Overview



Mineral Overview

- Naturally occurring
- Enzymatic reactions and baseline cellular function
- Powerful redox capacity
- Accumulation in tissues seems to be linked to aging processes
- In TBI
 - May be targets for pharmacology
 - May be targets for homeostasis

A**B**

Potassium

Sources: Fruits, vegetables, potatoes, legumes

Roles: Electrical conductance, muscular contraction, fluid balance

Recommended Intake: 3400mg for men, 2600mg for women

Toxicity: Muscle weakness, paralysis, cardiac arrhythmias

Deficiency: Hypertension, paralysis and encephalopathy if severe



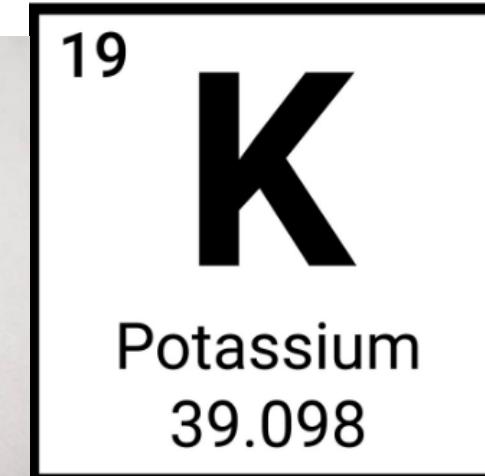
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Potassium
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Potassium

- Lindsey 2009: Trauma with TBI resulted in more hypokalemia than trauma alone
- Ngatuvasi 2023: HypoK ~ increased mortality rate and poor GOS
- Wu 2015: Severe hypoK is independent risk factor for mortality
- Reinert 2000: Intracerebral hyperK was associated with elevated ICP and mortality



Sodium

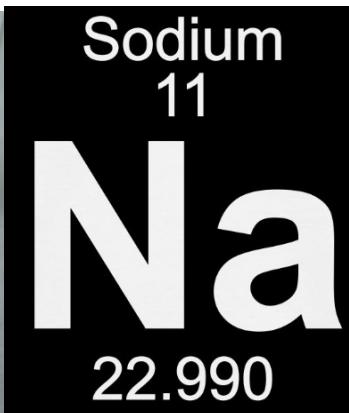
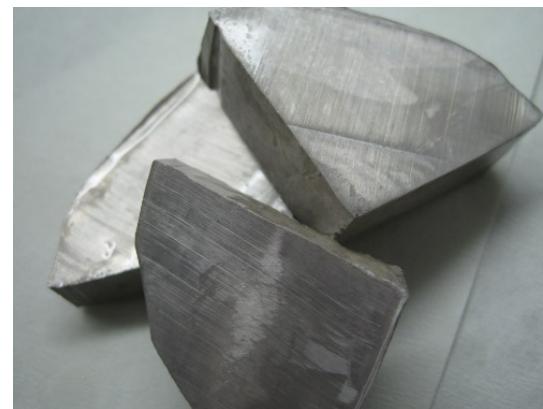
Sources: Table salt, packaged and prepared foods

Role: Muscle and nerve function, fluid balance

Recommended Intake: 1500 mg/day

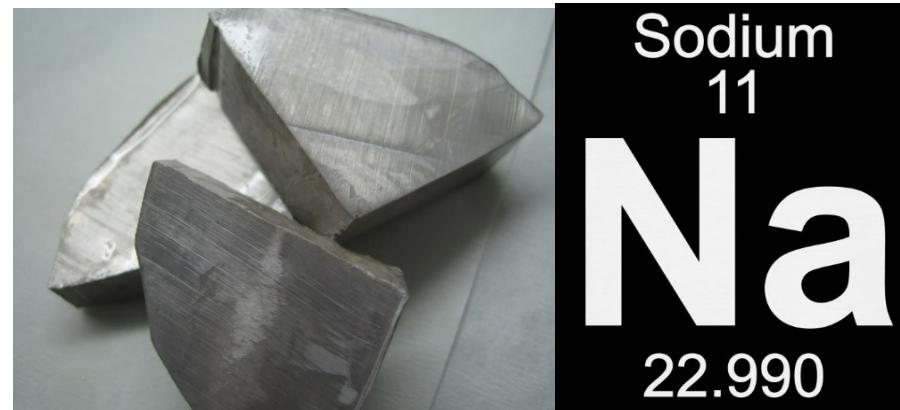
Toxicity: Hypertension, stroke, CV disease, headaches

Deficiency: Fatigue, confusion, headache, spasms, irritability, convulsions, cerebral edema



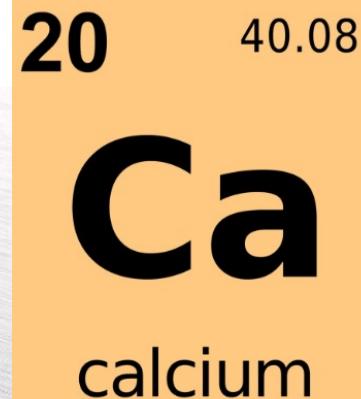
Sodium

- TBI
 - Acute care
 - Chronic sequelae
- Kolmodin 2013: HyperNa is associated with higher mortality
- Rajagopal 2017: Treated HypoNa improved LoS
- Ngatuvai 2023: HyperNa increased mortality rate and decreased GOS.
- Harrois 2020: Daily Na variability may predict 28-day mortality



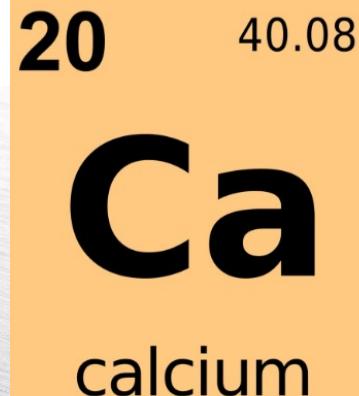
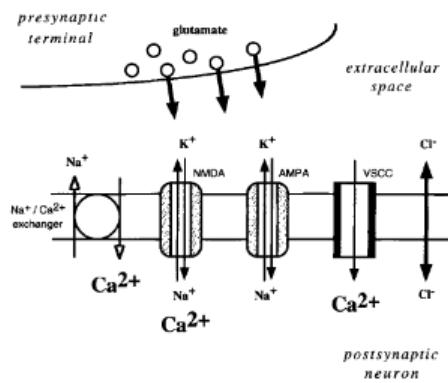
Calcium

- Sources: Dairy, seafood, vegetables, fortification in grains
- Role: Bones and teeth, clotting, muscle contraction heart rhythm
- Recommended Intake: 1000mg
- Toxicity: Rare, associated with cancer and CV disease
- Deficiency: Osteoporosis, Rickets disease, neuromuscular irritability



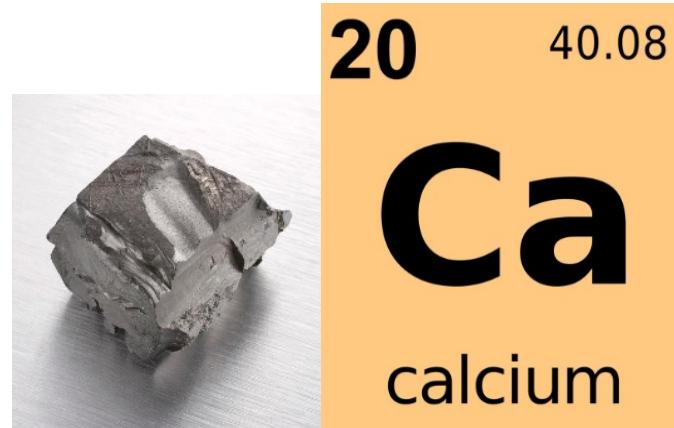
Calcium

- Traumatic Brain Injury
- Sustained influx of Ca^{++} may lead to cell death
- Ca^{++} mediated signaling pathways may be affected for prolonged periods of time following injury
- Other etiologies



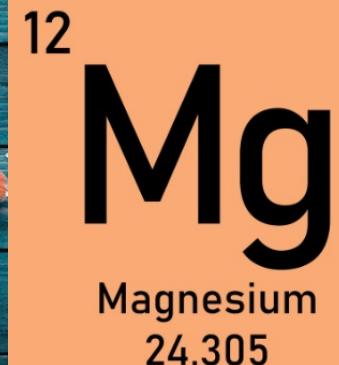
Calcium

- Vinos-Rios 2006: Hypocalcemia on day 3 following mod/severe injury may predict worsened mortality
- Badarni 2023: Mild hypocalcemia indicated favorable neurological outcomes
- Mekkodathil: HypoCa⁺⁺ does not predict mortality
- Ngatuva 2023: HypoCa⁺⁺ ~ increased mortality and poor GOS



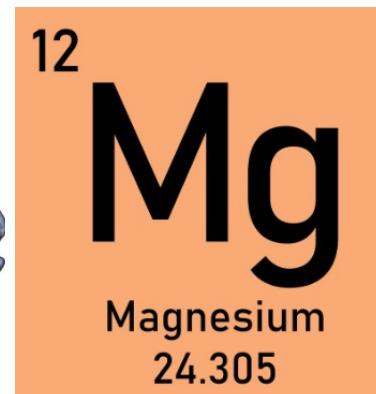
Magnesium

- Sources: Green leafy vegetables, nuts, seeds, whole grains
- Role: Bones/teeth, NM conduction, BP, cofactor for enzymes
- Recommended Intake: 420mg for men, 320mg for women
- Toxicity: Rare, diarrhea, depression, lethargy, cardiac arrhythmia/arrest
- Deficiency: Cramps, seizures, arrhythmia, nausea/vomiting



Magnesium

- HypoMg can increase intracellular Ca⁺⁺ flow resulting in more cell death
- Li 2006: Supplementation had no impact on mortality
- Mekkodathil 2023: HyperMg was independent predictor of mortality
- Ngatuvasi 2023: HypoMg ~ increased mortality rate and decreased GOS
- Stippler 2007: Low serum Mg and high CSF Mg were best predictors of poor outcomes in severe TBI

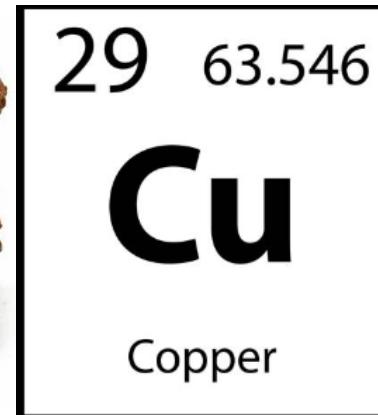


Electrolyte	Derangement	Mortality	GOS	ICU-LOS
Sodium	Hypernatremia	↑	-	↑
	Hyponatremia	-	↓	↑
Potassium	Hyperkalemia	-	-	-
	Hypokalemia	↑	-	-
Calcium	Hypercalcemia	-	-	-
	Hypocalcemia	↑	-	-
Magnesium	Hypermagnesemia	-	-	-
	Hypomagnesemia	-	↓	-

Ngatuva 2023

Copper

- Sources: Shellfish, seeds, nuts, organ meats, whole grains, chocolate
- Roles: Oxidative phosphorylation in mitochondria, connective tissue, nerve coverings, enzymes
- Recommended Intake: 900mcg daily
- Deficiency: Anemia, connective tissues disorders, osteoporosis, ataxia
- Toxicity: Wilson's disease, neurological and liver damage, GI symptoms, rare without genetic disease



Copper

- Tightly regulated
- Prominent stores in the cerebellum, basal ganglia, hippocampus, locus coeruleus
 - Brain contains 3rd largest store of Cu in the body
- Norepinephrine synthesis and wake/rest cycles
- Proposed as a potential therapeutic target for Alzheimer's
- Cu and ceruloplasmin tend to rise in acute or chronic inflammation
- Works closely with Zn for SOD function
- Too much → reactive oxygen species
- Too little → ceruloplasmin unstable and can't work with Zn



29	63.546
Cu	
Copper	

Copper

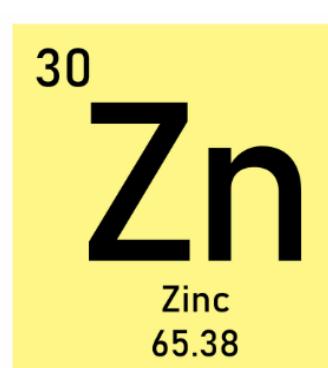
- Superoxide dismutase is upregulated in TBI
- Mikawa 1996, Kinouchi 1991: Zn/Cu SOD may be neuroprotective following TBI
- Isaev 2020: Proposed copper homeostasis as a potential target for TBI
- Jothari 2015: Serum Cu with prognostic utility?
- Peng 2015: PET/CT imaging with increased uptake of Cu
- Dash 2010: Low initial Cu and ceruloplasmin levels may predict elevated ICP
- Han 2018: Low ceruloplasmin/high Cu correlated with death & poor prognosis



29	63.546
Cu	
Copper	

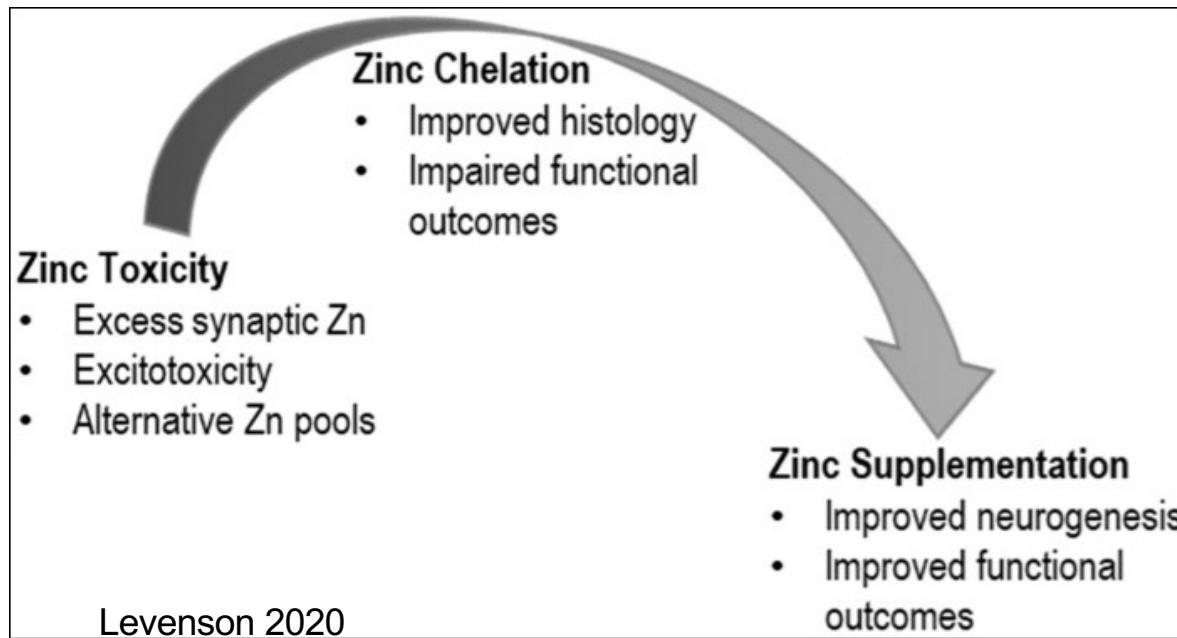
Zinc

- Sources: Oysters, meat, seafoods, tofu, legumes, nuts, dairy
- Recommended Intake: Men-11mg, Women-8mg
- Plays critical roles in the immune system and wound healing
 - Also DNA/RNA synthesis, enzymatic reactions
- Deficiency: Immune dysfunction, hypogonadism, oligospermia, emotional lability, anosmia, photophobia
- Toxicity:
 - Acute: nausea/vomiting, diarrhea, muscle cramps, abd pain
 - Chronic: Swayback syndrome-slow progression of neuropathy and anemia, fatigue, spasticity, gait abnormality

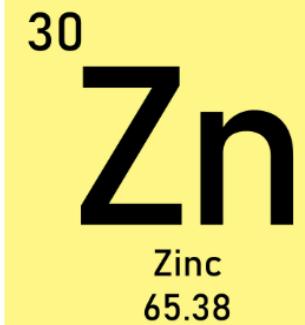


Zinc

Traumatic Brain Injury



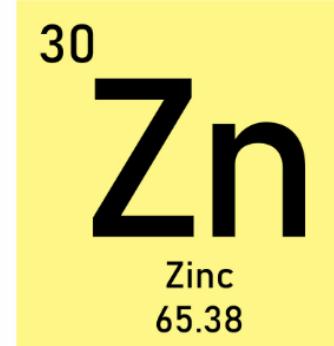
<1% bioavailable in serum



Zinc

Traumatic Brain Injury

- Young 1996: Zn supplementation improved GCS
- Khazdouz 2018: Zn supplementation improved GCS and LoS
- Cope 2011: Zn supplementation pre-injury
- TBI-adjacent
 - Swardfager 2013: depression is associated with a lower concentration of Zn in peripheral blood
 - Maes 1997: Antidepressant restored serum Zn levels
 - Lai 2012: Systematic review showed the same



Recommendations

- Zinc: Supplement iv acutely switching to po after 7 days
- Na: Management of sequelae affecting Na
- Potassium: Maintain normal range
- Magnesium: Maintain normal range
- Copper: Serum Cu close to acute injury may have prognostic value for ICH and mortality
- Calcium: Unclear in terms of prognostic value

Hopefully, you know should be able to:

- Identify current evidence and clinical practice guidelines on the supplementation of minerals and vitamins for Traumatic Brain Injury.
- Implement appropriate guidelines for vitamin and mineral supplementation for acute Traumatic Brain Injury
- Identify vitamin and mineral deficiencies, such as Wernicke's Encephalopathy, to prevent and treat these clinical entities.
- Any Questions?

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Thank you!

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