

Micronutrient Deficiencies and Supplements in Diabetes

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Diabetes and the Matter of Dietary Supplements

- **Dietary supplements** have gained attention among people with diabetes as an alternative and complementary treatment.
- These supplements, including **vitamins**, **minerals**, **herbal extracts**, and other **functional food ingredients**, are **believed to offer benefits**
 - ✓ Blood glucose regulation
 - ✓ Antioxidant properties
 - ✓ Anti-inflammatory effects

Diabetes and the Matter of Dietary Supplements

- Scientific evidence of their **effectiveness** and **safety** remains inconclusive.
- Usage **patterns**, **motivations**, and **influencing factors** among patients are not well understood.
- **More than 60%** of patients with diabetes reported using dietary supplements.
- **Only 45%** of individuals used dietary supplements based on medical advice.
- Common supplements included multivitamins, multimineral supplements, vitamin D, calcium, zinc, vitamin C, and fish oil

Micronutrient deficiencies in patients with diabetes

Meta-analysis of 132 studies with 52 501 participants:

- Micronutrient deficiencies are common in T2D patients.
- The pooled prevalence of **multiple micronutrient deficiency** (vitamins, minerals and electrolytes) was **45.30%** (95% CI 40.35% to 50.30%) among T2D patients.
- The pooled prevalence (48.62%, 95% CI 42.55 to 54.70) was higher in women.

Vitamin B Deficiency and supplementation in Diabetes

(B1, B3, B6, B9, B12)



Agenda

1. Essential roles of Vitamin B
2. Vitamin B (B1, B3, B6, B9, B12) deficiencies in patients with diabetes
3. Effects of Vitamin B supplementations in diabetes
4. What do Guidelines say?
5. Conclusion

Essential roles of Vitamin B:

- **Vitamin B1:**

- ✓ Cofactor for 3 key enzymes of glucose metabolism (Pyruvate dehydrogenase, α -ketoglutarate dehydrogenase, and trans ketolase)

- **Vitamin B3 (Niacin)**

- ✓ Coenzyme forms (NAD and NADP) are essential for carbohydrate, lipid, and protein metabolism

- **Vitamin B6 (Pyridoxal):**

- ✓ Transaminase activities and glycogen phosphorylation (gluconeogenesis and glycogenolysis)

Ge Y, et al. Am J Clin Nutr. 2023;117(2):426-435.

Dawood MH, Abdulridha MK, Qasim HS. J Med Life. 2023;16(10):1474-1481.

El-Khodary NM, Dabeas H, Werida RH. Nutr Diabetes. 2022;12(1):33.

Didangelos T, et al. Nutrients. 2021;13(2):395.

Essential roles of Vitamin B:

- **Vitamin B9 (Folic acid):**

- ✓ Regulating plasma Homocysteine (Hcy) concentration
 - Hyperhomocysteinemia in patients with diabetes → insulin resistance, dyslipidemia
- ✓ Preventing nitric oxide synthase dysfunction → improving endothelial dysfunction induced by high Homocysteine

- **Vitamin B12:**

- ✓ Synthesis and regeneration of myelin
- ✓ Analgesic action

Ge Y, et al. Am J Clin Nutr. 2023;117(2):426-435.

Dawood MH, Abdulridha MK, Qasim HS. J Med Life. 2023;16(10):1474-1481.

El-Khodary NM, Dabees H, Werida RH. Nutr Diabetes. 2022;12(1):33.

Didangelos T, et al. Nutrients. 2021;13(2):395.

Vitamin B Deficiency in Diabetes

- Lower serum levels of **vitamin B₁** (thiamine) was observed in patients with diabetes.
- Recommended Dietary Allowances (RDAs) for B1: 1.2 and 1.1 mg/d for adult men and women (1.4 mg/d for pregnancy and lactation)
- Thiamin is available in Multivitamin/mineral supplements with thiamin typically provide about 1.5 mg thiamin.
- The most commonly used forms of thiamin in supplements are **thiamin mononitrate and thiamin hydrochloride**, which are stable and water soluble

Association between diabetes and thiamine status - A systematic review and meta-analysis

Dan Ziegler^{a, *}, Karlheinz Reiners^b, Alexander Strom^a, Rima Obeid^c

Compared to non-diabetic controls, individuals with diabetes

- ↓ **Thiamine** (SMD = -0.97, 95% CI: -1.89 to -0.06)
- ↓ **Thiamine monophosphate** (SMD = -1.16, 95% CI: -1.82 to -0.50)
- ↓ **Total thiamine compounds** (SMD = -1.01, 95% CI: -1.48 to -0.54)
- ✓ Diabetes is associated with reduced levels of various thiamine markers.
- ✓ Individuals with diabetes **may have higher thiamine requirements**.

Vitamin B Deficiency in Diabetes

- **Deficiency of pyridoxine** is usually found in association with other vitamin B deficiencies, including folate (vitamin B9) and cobalamin (vitamin B12).
- Isolated pyridoxine deficiency is extremely rare.
- Recommended Dietary Allowances (RDAs) for B6: **1.3 mg/d for adults aged 19-50y** (1.9 and 2 mg/d for pregnancy and lactation), and 1.7 and 1.5 mg/d for men and women aged over 50y
- Vitamin B6 is available in multivitamins, in supplements containing other B complex vitamins, and as a stand-alone supplement
- The most common vitamin B6 in supplements is pyridoxine (in the form of pyridoxine hydrochloride).

Isolated Pyridoxine Deficiency Presenting as Muscle Spasms in a Patient With Type 2 Diabetes: A Case Report and Literature Review

- **Age/Sex:** 59-year-old female
- **Medical history:** Type 2 diabetes mellitus
- **Chief complaint:** Painful **muscle spasms** in both feet, spreading to legs and intermittently affecting the left arm
- **Symptoms not responsive to:** Baclofen and Cyclobenzaprine
- ↓ Plasma pyridoxal 5-phosphate: Confirmed pyridoxine deficiency
- Other vitamins (B1, B3, B12, folate): normal
- Standard-dose intramuscular pyridoxine injections for 3 weeks + **Oral pyridoxine supplements for 3 months**

**Consider evaluating vitamin B6 status in patients
with T2D with neuromuscular symptoms.**

Vitamin B Deficiency in Diabetes

- ↓ Serum folate in T2DM patients with neuropathy
- Recommended Dietary Allowances (RDAs) for Folate: 400µg/d for adults (500 and 600 µg/d for pregnancy and lactation)
- Folic acid is available in multivitamins, supplements containing other B-complex vitamins, and supplements containing only folic acid.
- Common doses ranges 400 to 800 µg folic acid in supplements for adults.

Mol Cell Endocrinol. 2017;443:72-79.

Folate. Fact Sheet for Health Professionals (<https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/>)

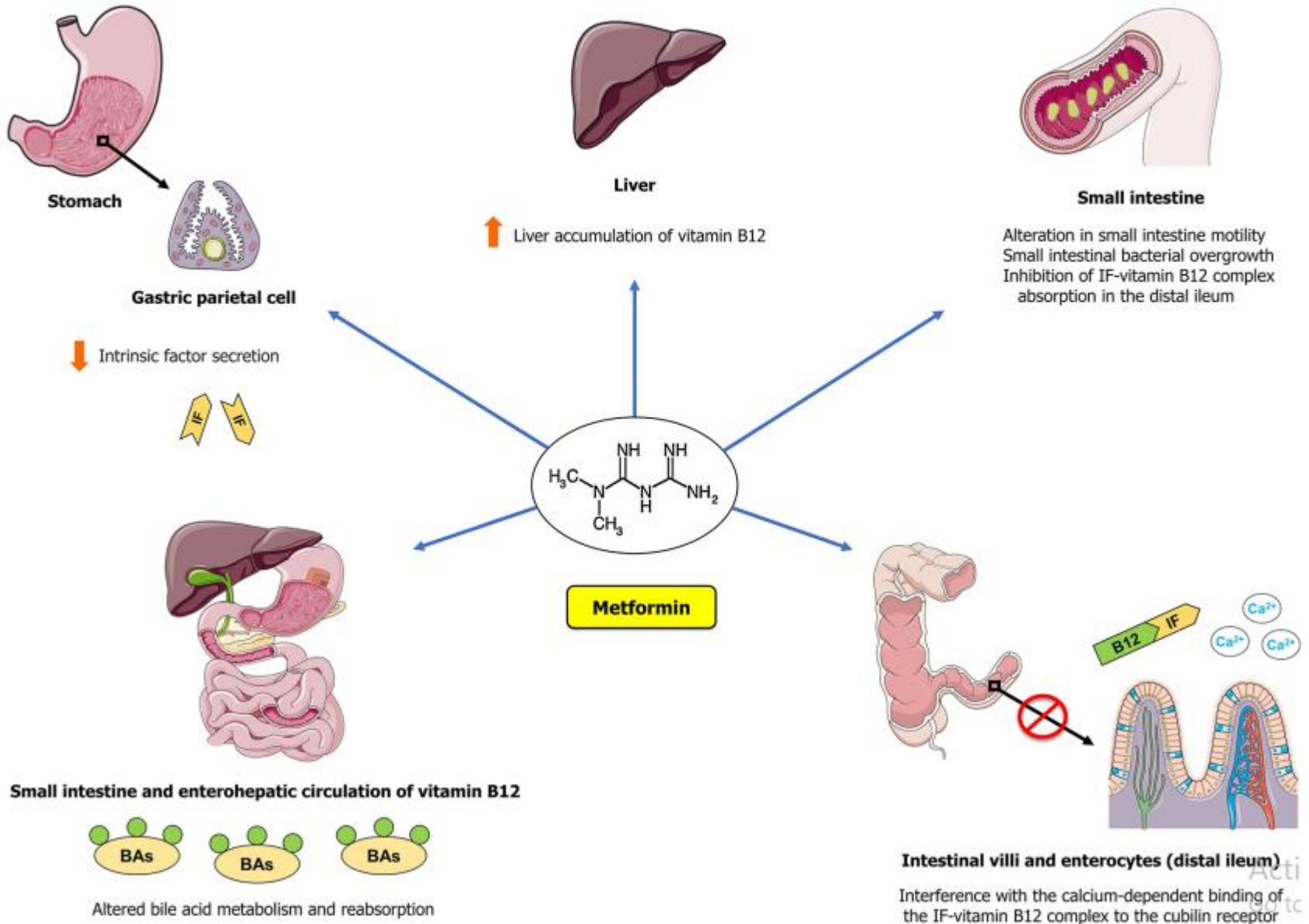
Vitamin B Deficiency in Diabetes

- **B12 deficiency:** 28.7% (95% CI: 21.1% to 36.4%)
- Meta-analysis of 26 studies:
 - ✓ Lower levels of vitamin B₁₂ in patients on metformin
 - ✓ Vitamin B12 deficiency is associated with metformin use, likely only in those with **longer/greater-dose**
- Recommended Dietary Allowances (RDAs) for Vitamin B12 in 2.4 µg/d for adults (2.6 and 2.8 in lactation and pregnancy, respectively)

Vitamin B Deficiency in Diabetes

- **Vitamin B12 Deficiency Risk:**
 - Metformin users had a **2.09 times higher risk** of vitamin B12 deficiency vs. non-users (95% CI 1.49-2.93).
- **Serum Vitamin B12 Levels:**
 - Metformin users had **significantly lower** vitamin B12 levels (mean difference **-63.7 pM**, 95% CI -74.35 to -53.05).
 - The decrease was **dose- and duration-dependent**.
- **Percentage Decrease in Vitamin B12:**
 - Metformin use led to a **14.7% greater decline** in vitamin B12 from baseline (95% CI -17.98% to -11.39%).

Metformin-induced vitamin B12 deficiency



Vitamin B Deficiency in Diabetes

Key Points on Defining Vitamin B12 Deficiency

- **No Consensus Exists:** There is **no universally accepted definition** for vitamin B12 deficiency
- **Debate Over Cut-off Values:**
 - Scientists disagree on the **exact serum B12 thresholds** for deficiency.
 - Different cut-offs can **underestimate or overestimate** deficiency rates
- **Current General Guidelines:**
 - **Sever deficiency:** Serum B12 < 148 pmol/L.
 - **Marginal/borderline deficiency:** Serum B12 148–221 pmol/L
- **Biomarker Challenges:**
 - Uncertainty remains about the **best biomarker (or combination)** to assess B12 status (e.g., **serum B12, methylmalonic acid, homocysteine**)

Vitamin B Deficiency in Diabetes

Clinical Manifestations of B12 deficiency

- **Hematologic signs:**
 - Megaloblastic anemia (hallmark feature)
 - Low WBC, RBC, and platelet counts
- **Neurological symptoms:**
 - Numbness, tingling in hands and feet
 - Can occur without anemia, risk of irreversible damage if untreated
- **Other symptoms:**
 - Glossitis (inflamed tongue)
 - Fatigue, palpitations, pale skin
 - Dementia, weight loss, infertility

Because the body stores about 1 to 5 mg vitamin B12 (~1000-2000 times as much as the amount typically consumed in a day), the symptoms of vitamin B12 deficiency can take several years to appear.

Effects of Supplementation with Vitamin B



Effects of supplementation

Vitamin B1 (thiamine):

- ✓ A meta-analysis of 6 trials:
- Supplementation with **100–900 mg/day of thiamine or benfotiamine** for up to 3 months:
 - Glycemic outcomes (HbA1c,FBG,Post Prandial Glucose): ↔
 - TG: ↓ (MD*=-1.1)
 - HDL-C: ↑ (MD=0.1)

*MD=Mean Difference

Muley A, et al. BMJ Open. 2022 Aug 25;12(8):e059834.

Effects of supplementation

- **Benfotiamine** is a synthetic S-acyl derivative of thiamine (vitamin B1).
- **Recommended in clinical guidelines:**
 - **Initial dose:** 120–600 mg/day.
 - **Maintenance dose:** 300 mg/day
- Targets both **painful and non-painful diabetic peripheral neuropathy** (DPN) symptoms.

Diabetes research and clinical practice. 2022;186:109063.
Exp Clin Endocrinol Diabetes. 2001;109(6):330-6.
Diabetes Care. 2010;33(10):2285-93.

Effects of supplementation

- **Benefits of Benfotiamine in DPN prevention:**

- Improves nerve conduction velocity.
- Reduces neuropathic pain, especially at higher doses

✓ Prevents motor nerve deficits

✓ Prevents AGE (advanced glycation end-product) formation

➤ Proposed as a first-line nutritional supplement (along with alpha-lipoic acid, ALA) for preventing DPN progression, given its efficacy and safety.

Diabetes research and clinical practice. 2022;186:109063.
Exp Clin Endocrinol Diabetes. 2001;109(6):330-6.
Diabetes Care. 2010;33(10):2285-93.

Effects of supplementation

Vitamin B3

- Niacin exists in two forms: **nicotinic acid** and **nicotinamide**.
- **Pharmacological Uses:** Nicotinic acid (1–3 g/day) effectively treats **dyslipidemia** but may impair glycemic control in diabetes.
- Nicotinamide is under investigation for diabetes prevention and treatment.
- **RDA:** 14 mg/day (women), 16 mg/day (men).
- **Mechanisms in Diabetes**
 - Protect pancreatic β -cells from autoimmune damage.
 - Maintain intracellular NAD levels.
 - Act as a weak antioxidant.

Effectiveness of niacin supplementation for patients with type 2 diabetes

A meta-analysis of randomized controlled trials

Dan Xiang, MM*, Qian Zhang, MM, Yang-Tian Wang, MM

2023

- 8 RCTs including 2,110 patients with T2D
- **No significant** effects were observed on glucose metabolism:
 - Plasma glucose: WMD = +0.18 mmol/L (95% CI: -0.14-0.50)
 - Hemoglobin A1c (HbA1c): WMD = +0.39% (95% CI: -0.15 to 0.94)

Effectiveness of niacin supplementation for patients with type 2 diabetes

A meta-analysis of randomized controlled trials

Dan Xiang, MM*, Qian Zhang, MM, Yang-Tian Wang, MM

2023

- 8 RCTs including 2,110 patients with T2D
- Niacin supplementation significantly improved lipid parameters:
 - ↓ Total cholesterol: WMD = -0.28 mmol/L (95% CI: -0.44 to -0.12)
 - ↓ Triglycerides: WMD = -0.37 mmol/L (95% CI: -0.52 to -0.21)
 - ↓ LDL cholesterol: WMD = -0.42 mmol/L (95% CI: -0.50 to -0.34)
 - ↑ HDL cholesterol: WMD = +0.33 mmol/L (95% CI: 0.21 to 0.44)

Effects of supplementation

Vitamin B6:

- No meta-analysis
- A randomized clinical trial, 129 Newly diagnosed Type2 Diabetes:
 - ✓ Metformin 500 mg/day+ vitamin B6 300 mg/day+ lifestyle modification
 - **FBS:** ↓36.89%
 - **HbA1c:** ↓ 16.69%
 - **Fasting Insulin:** ↓ 29.98%
 - **HOMA-IR:** ↓ 55.82%

Effects of supplementation

Vitamin B9 (Folic acid):

- A double-blind randomized controlled clinical trial:
 1. **Serum Homocysteine:** ↓28.2%
 2. **FBS:** ↓8.7%
 3. **HbA1c:** ↓8.2%
 4. **Serum insulin level:** ↓13.7%
 5. **Insulin resistance:** ↓ 21.7%

Sudchada P, et al. Diabetes Res Clin Pract. 2012 Oct;98(1):151-8.

Zhao JV, et al. Ann Epidemiol. 2018 Apr;28(4):249-257.e1.

El-Khodary NM, Dabees H, Werida RH. Nutr Diabetes. 2022;12(1):33.

Mokgalaboni K, et al. Nutr Diabetes. 2024 Apr 22;14(1):22.

Effects of supplementation

Vitamin B9 (Folic acid):

- Meta-analysis of 18 RCTs: 21,081 participants:
 1. **FBS:** ↓ (MD*=-0.15 mmol/l)
 2. **HOMA-IR:** ↓(MD=-0.83)
 3. **Serum insulin level:** ↓(MD=-1.94μIU/ml)
 4. **HbA1c:** ↔

*MD=Mean Difference

Sudchada P, et al. Diabetes Res Clin Pract. 2012 Oct;98(1):151-8.
Zhao JV, et al. Ann Epidemiol. 2018 Apr;28(4):249-257.e1.
El-Khodary NM, Dabees H, Werida RH. Nutr Diabetes. 2022;12(1):33.
Mokgalaboni K, et al. Nutr Diabetes. 2024 Apr 22;14(1):22.

Effects of supplementation

Vitamin B9 (Folic acid):

- Meta-analysis of 4 RCTs:
 1. **Serum Homocysteine:** ↓(WMD*=- 3.52 $\mu\text{mol/l}$)
 2. **HbA1c:** $\leftrightarrow$

*WMD=Weighted Mean Difference

Sudchada P, et al. Diabetes Res Clin Pract. 2012 Oct;98(1):151-8.
Zhao JV, et al. Ann Epidemiol. 2018 Apr;28(4):249-257.e1.
El-Khodary NM, Dabees H, Werida RH. Nutr Diabetes. 2022;12(1):33.
Mokgalaboni K, et al. Nutr Diabetes. 2024 Apr 22;14(1):22.

Effects of supplementation

Vitamin B12:

- A randomized double-blind placebo-controlled trial, 90 patients with type2 diabetes mellitus, using metformin for at least 4 years, with both peripheral and **Autonomic Diabetic Neuropathy** & **serum B12 level <400 pmol/l**:
 - ↑ Plasma vitamin B12 levels
 - Improvement of neurophysiological parameters

Conclusion

Thiamine supplementation:

- No effects on glycemic outcomes, ↓ Triglycerides, ↑ HDL

Niacin supplementation:

- [Niacin](#) supplements ranked best in [triglyceride](#) reductions and increasing high-density lipoprotein cholesterol levels with low to very low evidence certainty.

Vitamin B6 supplementation:

- Little evidence

Muley A, et al. BMJ Open. 2022 Aug 25;12(8):e059834.

Deng et al. 2023, Page 5201

Dawood MH, Abdulridha MK, Qasim HS. J Med Life. 2023;16(10):1474-1481.

Zhao JV, et al. Ann Epidemiol. 2018 Apr;28(4):249-257.

Mokgalaboni K, et al. Nutr Diabetes. 2024 Apr 22;14(1):22.

Conclusion

Folic acid supplementation:

- Benefits on insulin resistance, glycemic control, mitigating Cardio Vascular Diseases

Vitamin B12 supplementation:

- Monitoring and supplementation of vitamin B12 level are likely beneficial.

Muley A, et al. BMJ Open. 2022 Aug 25;12(8):e059834.

Deng et al. 2023, Page 5201

Dawood MH, Abdulridha MK, Qasim HS. J Med Life. 2023;16(10):1474-1481.

Zhao JV, et al. Ann Epidemiol. 2018 Apr;28(4):249-257.

Mokgalaboni K, et al. Nutr Diabetes. 2024 Apr 22;14(1):22.

Conclusion

- ✓ Potential deficiencies of micronutrient must be considered and corrected.
- ✓ The most prevalent vitamin B deficiency in T2D: **B12 deficiency**: 28.7% (95% CI: 21.1% to 36.4%)
- ✓ More studies must be conducted about the need for supplementation due to the conflicting results of studies to date

Conclusion

The American Diabetes Association:

- People at low risk for nutritional deficiencies meet their nutritional requirements with natural food sources.
- Do not generally support the use of micronutrient supplements for people with diabetes.

Conclusion

The American Diabetes Association:

- ✓ Dietary supplementation with vitamins, minerals (such as chromium and vitamin D), herbs, or spices (such as cinnamon or aloe vera) are not recommended for glycemic benefits.
- ✓ Health care professionals should inquire about intake of supplements and counsel as needed.

Conclusion

The American Diabetes Association:

- Counsel against β -carotene supplementation, as there is **evidence of harm** for specific individuals and **confers no benefits**.

Rich dietary sources of vitamin B



Top 10 Foods Highest in Thiamin (Vitamin B1)

1mg of Thiamin = 100% of the Daily Value (%DV)

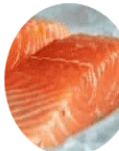
1 Lean Pork Chops



96% DV (1.1mg)
in a 6oz chop

332 calories

2 Fish (Salmon)



48% DV (0.6mg)
per 6oz fillet

350 calories

3 Flax Seeds



39% DV (0.5mg)
per oz

152 calories

4 Navy Beans



36% DV (0.4mg)
per cup

255 calories

5 Green Peas



35% DV (0.4mg)
per cup cooked

134 calories

6 Firm Tofu



33% DV (0.4mg)
per cup

363 calories

7 Brown Rice



30% DV (0.4mg)
per cup

248 calories

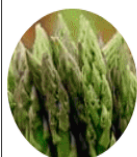
8 Acorn Squash



29% DV (0.3mg)
per cup cooked

115 calories

9 Asparagus



24% DV (0.3mg)
per cup cooked

40 calories

10 Mussels



21% DV (0.3mg)
per 3oz

146 calories

Top 10 Foods Highest in Vitamin B3 (Niacin)

16mg of Niacin = 100% of the Daily Value (%DV)

1 Tuna (Yellowfin)



234% DV (37.5mg)
in a 6oz fillet

221 calories

2 Lean Chicken Breast



100% DV (16.1mg)
in a 6oz breast

267 calories

3 Lean Pork Chops



85% DV (13.6mg)
in a 6oz chop

332 calories

4 Beef (Skirt Steak)



60% DV (9.5mg)
per 6oz steak

456 calories

5 Portabella Mushrooms



47% DV (7.6mg)
per cup sliced

35 calories

6 Brown Rice



32% DV (5.2mg)
per cup

248 calories

7 Peanuts (Dry Roasted)



25% DV (4.1mg)
per oz

167 calories

8 Avocados



22% DV (3.5mg)
per avocado

322 calories

9 Green Peas



20% DV (3.2mg)
per cup cooked

134 calories

10 Sweet Potatoes



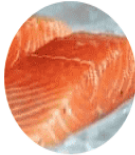
15% DV (2.4mg)
per cup mashed

258 calories

Top 10 Foods Highest in Vitamin B6

2mg of Vitamin B6 = 100% of the Daily Value (%DV)

1 Salmon



94% DV (1.6mg)
per 6oz fillet

309 calories

2 Lean Chicken Breast



92% DV (1.6mg)
in a 6oz breast

267 calories

3 Fortified Tofu



66% DV (1.1mg)
per cup

208 calories

4 Lean Pork Chops



54% DV (0.9mg)
in a 6oz chop

332 calories

5 Beef (Skirt Steak)



48% DV (0.8mg)
per 6oz steak

456 calories

6 Sweet Potatoes



35% DV (0.6mg)
per cup mashed

258 calories

7 Bananas



32% DV (0.6mg)
per cup sliced

134 calories

8 Potatoes



32% DV (0.5mg)
in a medium potato

161 calories

9 Avocados



30% DV (0.5mg)
per avocado

322 calories

10 Pistachio Nuts



28% DV (0.5mg)
per 1 oz handful

159 calories

Top 10 Foods Highest in Vitamin B9 (Folate)

400µg of Folate = 100% of the Daily Value (%DV)

1 Edamame (Green Soybeans)



121% DV (482µg)
per cup

188 calories

2 Lentils



90% DV (358µg)
per cup

230 calories

3 Asparagus



67% DV (268µg)
per cup cooked

40 calories

4 Spinach



66% DV (263µg)
per cup cooked

41 calories

5 Broccoli



42% DV (168µg)
per cup cooked

55 calories

6 Avocados



41% DV (163µg)
per avocado

322 calories

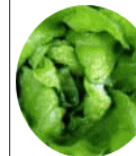
7 Mangos



18% DV (71µg)
per cup

99 calories

8 Lettuce



16% DV (64µg)
per cup

8 calories

9 Sweet Corn



15% DV (61µg)
per cup cooked

125 calories

10 Oranges



14% DV (54µg)
per cup

85 calories

Top 10 Foods Highest in Vitamin B12 (Cobalamin)

2µg of Vitamin B12 = 100% of the Daily Value (%DV)

1 Clams



3502% DV (84.1µg)
per 3oz serving

126 calories

2 Tuna



771% DV (18.5µg)
per 6oz fillet

313 calories

3 King Crab



642% DV (15.4µg)
in 1 crab leg

130 calories

4 Beef (Skirt Steak)



533% DV (12.8µg)
per 6oz steak

456 calories

5 Fortified Cereals



254% DV (6.1µg)
per 3/4 cup

95 calories

6 Fortified Soymilk



249% DV (6µg)
per 16oz glass

160 calories

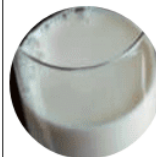
7 Fortified Tofu



137% DV (3.3µg)
per cup

208 calories

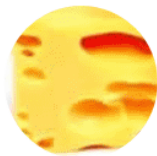
8 Low-Fat Milk



108% DV (2.6µg)
per 16oz glass

244 calories

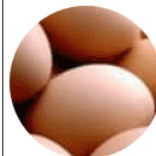
9 Swiss Cheese



36% DV (0.9µg)
per oz

112 calories

10 Eggs



23% DV (0.6µg)
in 1 large egg

78 calories



با تشکر از توجه شما