

# Drug-Induced Nutrient Depletion and Diabetic Therapy

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## **Introduction**

A challenge facing health care professionals in treating the pre-diabetic and diabetic patient today is the problem of complications arising from polypharmacy prescribing and resulting drug-induced metabolic imbalances. With approximately 48% of people in the United States taking prescription medications (up from 44% in the 1990s), patients with diabetes are placed a much higher risk for developing co-morbid conditions and for increasing disease pathologies.<sup>1</sup> Polypharmacy prescribing is now occurring in younger and younger patient populations, so it is becoming increasingly important to assess nutrient depletion risks as they relate to increased drug side-effects, future symptoms, co-morbid condition development or progression of the underlying disease itself.

### **Quick Facts<sup>2</sup>**

- Approximately 58% of diabetics take oral medications (2007-2009 National Health Interview Survey).
- Cardiovascular disease and stroke are listed on approximately 68% of diabetes-related death certificates among individuals aged 65 years or older.
- The risk for stroke is 2 - 4 times higher among individuals with diabetes.
- Approximately 73% of diabetics have hypertension and use prescription medications for hypertension.<sup>3</sup>
- A 2013 study (n=32,086, aged 40-60) reported that patients taking the following medications had a significant increase in developing type 2 diabetes.<sup>4</sup>
  - Statins
  - Thiazide diuretics
  - Beta-blockers
  - ACE inhibitors
  - ARBs
- Approximately 10-20% of patients with diabetes have pain associated with peripheral neuropathy, which affects the functionality, mood, and sleep patterns of these individuals.<sup>5</sup> The main classes of agents used to treat diabetic peripheral neuropathic pain include TCAs, anticonvulsants, SSRIs and opiates.

In the medical management of individuals with type 2 diabetes or co-morbid conditions, several classes of prescription drugs may be employed as therapies. These drugs increase the potential for depletion of nutrients that can potentially induce metabolic changes and further the progression of any component of the underlying diabetes or co-morbidities. It is of scientific interest and clinical concern that some of the reported side effects and adverse reactions of these commonly used medications in patients are actually manifestations of drug-nutrient depletion of these medications. Pharmaceuticals can

potentially inhibit nutrient absorption, synthesis, transport, storage, metabolism, or excretion of essential nutrients.

The chart below lists some of the most commonly used medications in the diabetic patient, including cardiovascular co-morbidity. Listed are some of the potential nutrient depletions associated with these drugs and some of the clinical effects often reported with the loss of one of these essential nutrients.

Drug	Potential Nutrient Depletion	Potential Health Consequence(s) of Nutrient Depletion
<b>Biguanides</b> <sup>6,7,8,9</sup> Metformin (Glucophage)	Coenzyme Q10 (CoQ10)	High blood pressure, congestive heart failure, muscle fatigue, joint and muscle aches, rhabdomyolysis, memory loss, gingivitis, muscle weakness, irregular heart beat, decreased immunity, insulin resistance
<b>Sulfonylureas</b> <sup>10</sup> Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Diabeta, Glynase, Micronase) Tolbutamide (Orinase) Tolazamide (Tolinase)	Coenzyme Q10 (CoQ10)	Hypertension Congestive heart failure Muscular and joint aches/fatigue Rhabdomyolysis Memory loss Gingivitis Imbalanced immunity Insulin resistance/Impaired glucose tolerance
<b>Beta-Blockers</b> <sup>11,12,13</sup> Propranolol (Inderal, Inderal LA) Metoprolol (Lopressor, Toprol, Toprol XL) Atenolol (Tenormin) Pindolol (Viskin) Bisoprolol (Monacor, Visken – w/HCTZ) Carvedilol (Coreg) Esmolol (Brevibloc) Labetelol (Normodyne) Naldolol (Corgard) Sotalol (Betapace) Timolol (Blocadren) Nebivolol (Bystolic)	Coenzyme Q10 (CoQ10)	Hypertension Congestive heart failure Muscular fatigue, weakness Joint and muscle aches Rhabdomyolysis Decreased cognitive function/memory loss Gingivitis Arrhythmia Imbalanced immunity, Insulin resistance/impaired glucose tolerance
	Melatonin	Sleep disturbances; insulin resistance/impaired glucose tolerance, cardiovascular problems imbalanced immune system; increased cancer risk, increased oxidative stress in the brain, decreased seizure threshold
	Zinc	Decreased immunity, decreased wound healing, smell and taste disturbances, anorexia, depression, night blindness, hair, skin and nail problems, menstrual irregularities, joint pain, nystagmus (involuntary eye movements), insulin resistance
<b>Thiazide Diuretics</b> <sup>14,15,16,17,18,19,20,21</sup>  Hydrochlorothiazide (HCTZ, HydroDiuril) Methclothiazide (Enduron) Indapamide (Lozol) Metolazone (Zaroxolyn)	Coenzyme Q10 (CoQ10)	High blood pressure Congestive heart failure Muscular/Joint fatigue/weakness Rhabdomyolysis Memory loss Gingivitis Irregular heart beat Decreased immunity Insulin resistance
	Magnesium	Muscle cramps Weakness Fatigue Insomnia Restless leg syndrome Irritability Anxiety Insulin resistance depression High blood pressure Cardiovascular problems Headaches

	Phosphorus	Decreases calcium absorption, osteoporosis, brittle bones
	Potassium	Arrhythmia, poor reflexes, muscle weakness, fatigue, thirst, confusion, constipation, dizziness, nervousness
	Sodium	Muscle weakness, poor concentration, memory loss, dehydration, loss of appetite
<b>Loop Diuretics</b> <sup>22,23,24,25,26</sup> Bumetanide (Bumex) Ethacrynic Acid (Edecrine) Furosemide (Lasix)	Calcium	Osteoporosis, heart & blood pressure problems, back or leg pain, nervousness, tooth decay
	Magnesium	Muscle cramps, weakness, fatigue, insomnia, restless leg syndrome, irritability, anxiety, insulin resistance, depression, high blood pressure, cardiovascular problems, headaches
	Potassium	Irregular heart beat, poor reflexes, muscle weakness, fatigue, thirst, confusion, constipation, dizziness, nervousness
	Sodium	Muscle weakness, poor concentration, memory loss, dehydration, loss of appetite
	Vitamin B1 (Thiamine)	Depression, irritability, memory loss/confusion, indigestion, weight loss/anorexia, swelling, muscle weakness, irregular heart beat, fatigue, numbness and tingling
	Vitamin B6 (Pyridoxine)	Depression, sleep disturbances, nerve inflammation, PMS, lethargy, decreased alertness, anemia, altered mobility, elevated homocysteine, nausea, vomiting, and seborrheic dermatitis
	Vitamin C	Loss of antioxidant potential, increased capillary fragility, muscle weakness, poor wound healing, bleeding gums, anemia, poor appetite, tender and swollen joints
	Zinc	Decreased immunity, decreased wound healing, smell and taste disturbances, anorexia, depression, night blindness, hair, skin and nail problems, menstrual irregularities, joint pain, nystagmus (involuntary eye movements), insulin resistance
<b>Potassium Sparing Diuretics</b> <sup>27,28</sup>	Calcium	Osteoporosis, heart & blood pressure problems, back or leg pain, nervousness, tooth decay

<b>Potassium Sparing Diuretics</b> <sup>27,28</sup> Triamterene (Diurenum) Triamterene and HCTZ (Dyazide, Maxide) Spironolactone (Aldactone)	Calcium	Osteoporosis, heart & blood pressure problems, back or leg pain, nervousness, tooth decay
	Folic Acid	Birth defects, cervical dysplasia, anemia, heart disease, elevated homocysteine, headaches, fatigue, insomnia, diarrhea, nausea, increased cancer risk, decreased methylation
	Zinc	Decreased immunity, decreased wound healing, smell and taste disturbances, anorexia, depression, night blindness, hair, skin and nail problems, menstrual irregularities, joint pain, nystagmus (involuntary eye movements), insulin resistance
<b>Miscellaneous Diuretics</b> <sup>29,30</sup> Chlorthalidone (Hygroton, Thalidone)	Magnesium	Muscle cramps, weakness, fatigue, insomnia, restless leg syndrome, irritability, anxiety, insulin resistance, depression, high blood pressure, cardiovascular problems, headaches
	Phosphorus	Decreases calcium absorption, osteoporosis, brittle bones
	Potassium	Arrhythmia, poor reflexes, muscle weakness, fatigue, thirst, confusion, constipation, dizziness, nervousness
	Sodium	Muscle weakness, poor concentration, memory loss, dehydration, loss of appetite
	Zinc	Decreased immunity, decreased wound healing, smell and taste disturbances, anorexia, depression, night blindness, hair, skin and nail problems, menstrual irregularities, joint pain, nystagmus, insulin resistance
<b>ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors)</b> <sup>31,32</sup> Captopril (Capoten) Enalapril (Vasotec) Lisinopril (Zestril, Prinivil) Ramipril (Altace)	Zinc	Decreased immunity, decreased wound healing, smell and taste disturbances, anorexia, depression, night blindness, hair, skin and nail problems, menstrual irregularities, joint pain, nystagmus (involuntary eye movements), insulin resistance.
	Sodium	Muscle weakness, poor concentration, memory loss, dehydration, loss of appetite
<b>ARBs (Angiotensin II Receptor Antagonists)</b> <sup>33,34</sup> Losartan (Cozaar) Valsartan (Diovan) Telmisartan (Micardis) Irbesartan (Avapro) Azilsartan (Edarbi) Olmesartan (Benicar)	Zinc	Decreased immunity, decreased wound healing, smell and taste disturbances, anorexia, depression, night blindness, hair, skin and nail problems, menstrual irregularities, joint pain, nystagmus (involuntary eye movements), insulin resistance.

<b>HMG-CoA Reductase Inhibitors</b> <sup>35,36,3738,39,40,41,42</sup>  Atorvastatin (Lipitor) Lovastatin (Mevacor, Altocor) Fluvastatin (Lescol) Pravastatin (Pravachol) Simvastatin (Zocor)	Coenzyme Q10 (CoQ10)	High blood pressure, congestive heart failure, fatigue, gingivitis, muscle weakness, irregular heartbeat, decreased immunity
	Vitamin E	Dry skin, dry hair, anemia, easy bruising, PMS, eczema, dermatitis, psoriasis, muscle weakness, decreased antioxidant capacity, poor wound healing/impaired immunity
	Vitamin D	Osteoporosis, increased risk of skeletal fractures, hearing difficulties, depression, hormonal imbalances, muscular weakness, hypertension, autoimmune diseases, multiple sclerosis, diabetes, schizophrenia and decrease immunity
	Carnitine	Elevated blood lipids, abnormal liver function, muscle weakness, fatigue, blood sugar imbalances, increased risk of cardiovascular disease
	Omega-3 fatty acids	Neurochemical imbalances, skin disorders, chronic inflammation, heart and blood vessel disorders, immune imbalances, autoimmune conditions, memory and cognitive impairment, joint and muscle pain, insulin resistance and increased risk of type2 diabetes, increased risk of cancer
	Zinc	Decreased immunity, decreased wound healing, smell and taste disturbances, anorexia, depression, night blindness, hair, skin and nail problems, menstrual irregularities, joint pain, nystagmus (involuntary eye movements), insulin resistance.
	Selenium	Decreased antioxidant protection, muscle aches, decreased immunity, red blood cell fragility, fatigue, anemia, and decreased conversion of T4 to T3.
	Copper	Hair color loss, anemia, fatigue, low body temperature, cardiovascular problems, nervous system disorders, decreased immunity
	Testosterone	Increased mortality in men with CHD Insomnia Insulin resistance/Impaired glucose tolerance Obesity Type 2 diabetes Thyroid hormone imbalances Alzheimer's disease Osteoporosis/decreased bone mineral density Immune imbalances

<b>Bile Acid Sequestrants</b> <sup>43,44</sup> Cholestyramine (Questran)	Beta-carotene (Vitamin A)	Decreased immunity, night blindness, dry skin, brittle nails
	Calcium	Osteoporosis, heart and blood pressure problems, back or leg pain, nervousness, tooth decay
	Folic Acid	Birth defects, cervical dysplasia, anemia, heart disease, elevated homocysteine, headaches, fatigue, insomnia, diarrhea, nausea, increased cancer risk, decreased methylation
	Iron	Anemia, fatigue, hair loss, brittle nails, decreased thyroid hormone production
	Magnesium	Muscle cramps, weakness, fatigue, insomnia, restless leg syndrome, irritability, anxiety, insulin resistance, depression, high blood pressure, cardiovascular problems, headaches
	Phosphorus	Decreases calcium absorption, osteoporosis, brittle bones
	Vitamin B12	Fatigue, peripheral neuropathy, macrocytic anemia, depression, memory loss/confusion, easy bruising, loss of appetite, nausea, vomiting, increased cardiovascular disease risk, increased homocysteine levels, decreased methylation
	Vitamin D	Osteoporosis, increased risk of skeletal fractures, hearing difficulties, depression, hormonal imbalances, muscular weakness, hypertension, autoimmune diseases, multiple sclerosis, diabetes, schizophrenia and decrease immunity
	Vitamin E	Dry skin, dry hair, anemia, easy bruising, PMS, eczema, dermatitis, psoriasis, muscle weakness, decreased antioxidant capacity, poor wound healing/impaired immunity
	Vitamin K	Easy bleeding, osteoporosis and brittle bones
	Zinc	Decreased immunity, decreased wound healing, smell and taste disturbances, anorexia, depression, night blindness, hair, skin and nail problems, menstrual irregularities, joint pain, nystagmus (involuntary eye movements), insulin resistance
<b>Colestipol (Colestid, Welchol)</b> <sup>45,46</sup>	Beta-carotene (Vitamin A)	Decreased immunity, night blindness, dry skin, brittle nails
	Folic Acid	Birth defects, cervical dysplasia, anemia, heart disease, elevated homocysteine, headaches, fatigue, insomnia, diarrhea, nausea, increased cancer risk
	Iron	Anemia, fatigue, hair loss, brittle nails
	Vitamin B12	Fatigue, peripheral neuropathy, macrocytic anemia, depression, memory loss/confusion, easy bruising, loss of appetite, nausea, vomiting, increased cardiovascular

	Vitamin B12	Fatigue, peripheral neuropathy, macrocytic anemia, depression, memory loss/confusion, easy bruising, loss of appetite, nausea, vomiting, increased cardiovascular disease risk, increased homocysteine levels, decreased methylation.
	Vitamin E	Dry skin, dry hair, anemia, easy bruising, PMS, eczema, dermatitis, psoriasis, muscle weakness, decreased antioxidant capacity, poor wound healing/impaired immunity
	Coenzyme Q10 (CoQ10)	High blood pressure, congestive heart failure, muscular fatigue, joint and muscle aches, rhabdomyolysis, memory loss, gingivitis, muscle weakness, irregular heart beat, decreased immunity, insulin resistance
<b>Fibrates</b> <sup>47,48</sup> Fenofibrate (Tricor) Gemfibrozil (Lopid)	Vitamin E	Dry skin, dry hair, anemia, easy bruising, PMS, eczema, dermatitis, psoriasis, muscle weakness, decreased antioxidant capacity, poor wound healing/impaired immunity
	Coenzyme Q10 (CoQ10)	High blood pressure, congestive heart failure, muscular fatigue, joint and muscle aches, rhabdomyolysis, memory loss, gingivitis, muscle weakness, irregular heart beat, decreased immunity, insulin resistance
	Vitamin D	Osteoporosis, increased risk of skeletal fractures, hearing difficulties, depression, hormonal imbalances, muscular weakness, hypertension, autoimmune diseases, multiple sclerosis, schizophrenia and decrease immunity
	DHEA	Increased risk of developing Type 2 diabetes, heart disease, cancer, osteoporosis, depression, obesity, decreased immune function, loss of strength and muscle mass, and memory problems like Alzheimer's disease, high blood pressure, elevated cholesterol levels, and increased platelet aggregation, increased risk of thrombosis
<b>Opiate Pain Medications</b> Morphine Hydrocodone (Lortab, Vicodin) Oxycodone (Percocet,	Folic Acid	Birth defects, cervical dysplasia, anemia, heart disease, elevated homocysteine, headaches, fatigue, insomnia, diarrhea, nausea, increased cancer risk, decreased methylation



<p><b>Tricyclic Antidepressants (TCAs)</b>  Amitriptylline (Elavil)  Imipramine (Tofranil)  Clomipramine (Anafranil)  Desipramine (Norpramin)  Nortriptylline (Aventyl, Pamelor)  Doxepin (Sinequan)  Protriptylline (Vivactil)</p>	<p>Vitamin B12</p>	<p>Fatigue, peripheral neuropathy, macrocytic anemia, depression, memory loss/confusion, easy bruising, loss of appetite, nausea, vomiting, increased cardiovascular disease risk, decreased methylation</p>
<p><b>Selective Serotonin Reuptake Inhibitors (SSRIs)</b>  Citalopram (Celexa)  Escitalopram (Lexapro)  Fluvoxamine (Luvox)  Paroxetine (Paxil)  Fluoxetine (Prozac)  Sertraline (Zoloft)  Desvenlafaxine (Pristique)</p>	<p>Melatonin</p>	<p>Sleep disturbances that may lead to insulin resistance and cardiovascular problems and a weakened immune system; increased cancer risk, increased oxidative stress in the brain, decreased seizure threshold.</p>
	<p>Tryptophan</p>	<p>Neurochemical imbalances, anxiety, depression, other psychiatric disorders, insomnia and sleep disturbances, food cravings</p>
<p><b>Non-Steroidal Anti-inflammatory Drugs (NSAIDs) COX-1 inhibitors<sup>49,50,51</sup></b></p> <p><b>Including:</b>  Diclofenac (Cataflam, Voltaren)  Diflunisal (Dolobid)  Etodolac (Lodine, Lodine XL)  Fenoprofen calcium (Nalfon)  Flurbiprofen (Ansaid)  Ibuprofen (Advil, Motrin)  Ketoprofen (Actron, Orudis, Orudis KT, Oruvail)  Meclofenamate sodium (Meclomen)  Mefenamic acid (Ponstel)  Meloxicam (Mobic)  Nabumetone (Relafen)  Naproxen (Alleve, Naprosyn)  Oxaprozin (Daypro)  Piroxicam (Feldene)  Sulindac (Clinoril)  Tolmetin sodium (Tolectin)</p>	<p>Tryptophan</p>	<p>Neurochemical imbalances, anxiety, depression, other psychiatric disorders, insomnia and sleep disturbances, food cravings</p>
	<p>Melatonin</p>	<p>Sleep disturbances that may lead to insulin resistance and cardiovascular problems and a weakened immune system; increased cancer risk, increased oxidative stress in the brain, decreased seizure threshold</p>
	<p>Sodium</p>	<p>Muscle weakness, poor concentration, memory loss, dehydration, loss of appetite</p>
	<p>Zinc</p>	<p>Decreased immunity, decreased wound healing, smell and taste disturbances, anorexia, depression, night blindness, hair, skin and nail problems, menstrual irregularities, joint pain, nystagmus (involuntary eye movements), insulin resistance</p>
	<p>DHEA</p>	<p>Fatigue, weight gain, depression, bone loss, musculoskeletal pain, immune imbalances, sleep disturbances</p>
<p><b>Acetaminophen<sup>52,53</sup></b> (Tylenol)</p>	<p>Glutathione</p>	<p>Decreased antioxidant capacity, liver damage, sweating, fatigue, decreased immunity, hair loss, dry skin, itching.</p>

## Conclusion

In the diabetic patients, complications arising from drug therapy can hinder the ability of clinicians achieving desired outcomes in these individuals. Monitoring of prescribing habits and recognizing the potential for drug-induced nutrient depletion and drug-induced diseases can make the difference between enhanced outcomes and improved quality of life.

**DISCLAIMER:** Statements made are for educational purposes and have not been evaluated by the US Food and Drug Administration. They are not intended to diagnose, treat, cure, or prevent any disease. If you have a medical condition or disease, please talk to your doctor prior to using the recommendations given.

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