An integrative medicine approach to managing nutrient depletions in the cardiometabolic patient

Keywords

Cardiometabolic disease

Nutritient depletion

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Abstract

This article presents a further exploration of the risk factors underlying cardiometabolic (CM) disease and their identification and management within an integrative medicine framework as illustrated by the case of a 30-year-old obese African American male who presented for a follow-up visit with regard to his metabolic syndrome (MeS).

This article reviews in detail the pathophysiology of common nutrient depletions and their contribution to CM disease risk, as well as drug-induced nutrient depletions incurred during treatment for CM disease and the MeS. The review also includes a detailed discussion on the evaluation and treatment of nutrient deficiencies.

The article concludes with a detailed discussion of the case resolution. Following an extensive metabolic evaluation, a program of specific nutrient repletion was instituted alongside testosterone replacement therapy in addition to instituting stress reduction techniques and herbal supplements to improve his physiologic stress response. The patient returned to clinic after 3 months to review progress and laboratory results. He had lost 15 pounds, reported increased energy levels, and complete elimination of joint aches. He was scheduled to return to the clinic after a further 3 months for re-evaluation.

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Online 24 April 2010

Case

A 30-year-old obese African American male with a body mass index (BMI) of 36 presented for a follow-up visit with regard to his metabolic syndrome (MeS). At a prior visit, he was encouraged to lose weight and begin an exercise program. At the latest visit, he also complained of generalized joint aches for which he self-medicates with ibuprofen as needed. He had a waist circumference of 46 inches, blood pressure 138/89, fasting blood glucose 110 mg/dl, fasting insulin 36 μU/ml, high-sensitivity CRP (hs-CRP) 4.5 mg/l (elevated risk), total cholesterol 235 mg/dl (LDL 160 mg/dl, HDL 39 mg/dl), and triglycerides 174 mg/dl. His comprehensive metabolic panel was otherwise unremarkable. There is a history of premature coronary heart disease in his father and older brother, and his parents and two older brothers suffer from diabetes and several related complications. The patient reported that his busy work schedule and increase in business travel have precluded him from adhering to a proper dietary and exercise regimen.

Since the patient has been unable to voluntarily improve his health, drug intervention is likely necessary. According to current

guidelines for the management of MeS and its inherent components, this patient could potentially be started on any or all of the drugs listed in Table 1, below [1]. If necessary, he was also amenable to the addition of non-pharmacologic therapies, including specific nutrients that could potentially improve or reverse his metabolic syndrome as he continued his attempts at lifestyle modification.

Background

Cardiometabolic Disease and Nutrient Depletion

This case represents a further exploration of the risk factors underlying cardiometabolic (CM) disease and their identification and management within an integrative medicine

Table 1 Drugs commonly used in individuals with cardiometabolic risks and known nutrient depletions

Drug	Potential health consequence / side effects of drugs	Potential nutrient loss	Effects of nutrient depletion
THIAZIDE DIURETICS Including: Hydrochlorothiazide (HCTZ) Methyclothiazide (Enduron®) Indapamide (Lozol®) Metolazone (Zaroxolyn®)	*Short-term:* Nervousness/anxiousness Fatigue Increased urinary voiding Diarrhea Dizziness Loss of appetite Nausea/vomiting Headache Dry mouth and mucous membranes Constipation *Long-term*: Irregular heart beat (arrythmias) Breathing difficulty Numbness/tingling in extremities Confusion Nervousness Fatigue Muscle cramps Mood changes Blurred vision Poor wound healing Lowered immunity Increased risk of osteoporosis Cardiovascular problems Increased risk of birth defects	Coenzyme Q10 Magnesium Phosphorus Potassium Sodium Zinc	**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 **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 **Phosphorus** - Decreases calcium absorption, osteoporosis, brittle bones **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 (involuntary eye movements), insulin resistance

Table 1 (*Continued*)

Drug	Potential health consequence / side effects of drugs	Potential nutrient loss	Effects of nutrient depletion
HMG-CoA REDUCTASE INHIBITORS Including: Atorvastatin (Lipitor®) Lovastatin (Mevacor®) Fluvastatin (Lescol®) Pravastatin (Pravachol®) Simvastatin (Zocor®)	*Short-term*: Nausea/vomiting Diarrhea Gas/bloating Blurred vision Constipation Heartburn Headache Dizziness *Long-term*: Elevated liver enzymes Muscle pain/ weakness Memory loss Kidney failure	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
ACE INHIBITORS: Including: Captopril (Capoten®) Enalopril (Vasotec®) Ramipril (Altace®) Quinapril (Accupril®) Lisinopril (Prinivil®, Zestril®) Benazepril (Lotensin®)	*Short-term*: Facial flushing Nausea/vomiting Headache Cough Insomnia Nasal congestion Sexual dysrfunction *Long-term*: Swelling (edema) Low blood pressure (hypotension) Kidney problems Increased potassium levels, which can lead to irregular heart beat (arrythmias) Immune imbalances	Zinc	**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

Table 1 (*Continued*)

Drug	Potential health consequence / side effects of drugs	Potential nutrient loss	Effects of nutrient depletion
BETA-BLOCKERS: Including: Propranolol (Inderal®) Metoprolol (Toprol®, Lopressor®) Atenolol (Tenormin®) Pindolol (Visken®) Acebutolol (Sectral®) Betaxolol (Kerlone®) Bisoprolol (Ziac®) Carteolol (Cartrol®) Carvedilol (Coreg®) Esmolol (Brevibloc®) Labetalol (Normodyne®, Trandate®) Nadolol (Corgard®) Sotalol (Betapace®) Timolol (Blocadren®)	*Short-term*: Nausea/vomiting Diarrhea Fatigue Dry mouth Dizziness Visual disturbances Headache Sexual side effects Breathing difficulties Insomnia Nightmares Irregular heart beat (arrhythmia) *Long-term*: Depression Sexual side effects Decreased HDL, the ''good'' cholesterol Fatigue Blood sugar imbalances Increased risk of heart attack/stroke Increased risk of type 2 diabetes	Coenzyme Q10 Melatonin	**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 **Melatonin** - 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.
HYPOGLYCEMIC DRUGS: BIGUANIDES Metformin (Glucophage) COMBINATION DRUGS WITH METFORMIN: Glucotrol/metformin (Glucovance) Glipizide/metformin (Metaglip) Glitazones/metformin (Avandamet)	*Short-term:* Diarrhea Dizziness Drowsiness Fatigue Anxiety Headache Nausea Weight gain/hunger increase Fullness Heartburn Gas/bloating Hypoglycemia Edema (swelling) *Long-term:* Hypoglycemia Muscle weakness Tremor	Coenzyme Q10 Folic acid Vitamin B12	**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 **Folic acid** - Birth defects, cervical dysplasia, anemia, heart disease, elevated homocysteine, headaches, fatigue, insomnia, diarrhea, nausea, increased cancer risk, decreased methylation **Vitamin B12** - Fatigue, peripheral neuropathy, macrocytic anemia, depression, memory loss/confusion, easy bruising, loss of appetite, nausea, vomiting, increased cardiovascular disease risk, decreased methylation

Table 1 (*Continued*)

Drug	Potential health consequence / side effects of drugs	Potential nutrient loss	Effects of nutrient depletion
SULFONYLUREAS: Including: Acetohexamide (Dymelor®) Glyburide (Micronase®, Diabeta®), Glipizide (Glucotrol), Tolazamide (Tolinase®)	*Short-term*: Dizziness Drowsiness Fatigue Anxiety Headache Nausea Weight gain/hunger increase Fullness Heartburn Gas/bloating Hypoglycemia Edema (swelling)	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
s	*Long-term*: Hypoglycemia Muscle weakness Tremor Sleep disturbances Depression Irregular heart beat		
ANTI- INFLAMMATORY DRUGS			
Non-Steroidal Anti-inflammatory Drugs (NSAIDs) COX-1 inhibitors Including: 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)	*Short-term:* GI ulcers Abdominal burning/ pain/cramping Nausea/vomiting Diarrhea Constipation Fluid retention (edema) Dizziness Rash Shortness of breath (especially asthmatics) *Long-term:* Fatigue Liver and kidney damage Gastrointestinal bleeding Intestinal damage/dysbiosis Increased risk of birth defects	Folic Acid	**Folic acid** - Birth defects, cervical dysplasia, anemia, heart disease, elevated homocysteine, headaches, fatigue, insomnia, diarrhea, nausea, increased cancer risk, decreased methylation

Adapted from: Drug Induced Nutrient Depletion Handbook (2001) [82].

framework. It is also important to recognize the potential for abnormalities in serum insulin, testosterone and cortisol levels as they relate to MeS. This article reviews in detail common nutrient depletions and their contribution to CM disease risk, including:

(1) Magnesium
(2) Chromium
(3) Vitamin D
(4) Coenzyme Q10 (CoQ10)

The risk factors associated with CM disease portend an increased risk for the development of Type 2 diabetes and cardiovascular disease. CM disease represents an expansion of MeS, including excess inflammatory mediators (e.g. interleukin (IL)-6, tumor necrosis factor (TNF)-α, leptin, adiponectin, high sensitivity C-reactive protein (hs-CRP)), nutritional deficiencies, hypercoagulability (plasminogen activator inhibitor (PAI-1), fibrinogen), oxidative stress, environmental toxins (e.g. smoking, pesticide and heavy metal contamination), genetic polymorphisms, poor lifestyle habits, disrupted sleep, hormonal derangements, and psychosocial stress in addition to race, gender, age and family genetics.

Integrative Medicine

Integrative medicine is an evidence-based combination of conventional, alternative, and complementary therapies. It utilizes conventional medicine and surgery in combination with herbs, supplements, manual therapies, mind–body techniques and other modalities to allow patients to achieve optimal health and healing while being actively involved in their own care [2].

Data from the 2007 National Health Interview Survey (NHIS), estimates that US adults spent approximately $33.9 billion out-of-pocket on visits to complementary medicine practitioners and on purchases of supplement products, educational classes, and other materials [3]. This number equals approximately 1.5% of total healthcare expenditures in the US and 11.2% of out-of-pocket healthcare expenditures. The Centers for Disease Control NHIS data indicate that the US public makes more than 300 million visits to integrative providers each year and spends billions of dollars. Due to the negative stigma associated with ''non-traditional'' treatment approaches, 70% of patients do not tell their physician about their use of integrative approaches [4]. It is of the utmost importance that physicians understand the need for, and the complexities of using, Integrative Medicine as part of CM risk therapeutics.

Pathophysiology of Nutrient Deficiencies and Cardiometabolic Risk

Patients suffering from CM disease may be deficient in essential nutrients secondary to poor dietary intake, the underlying health condition itself, drug-induced nutrient depletion, and stress. Typically, patients with insulin resistance and type 2 diabetes suffer from suboptimal serum levels of chromium, magnesium, and zinc [5,6]. In addition, vitamin D deficiency is frequently seen and has been associated with hypertension, hyperglycemia, and metabolic syndrome [7,8]. These nutritional deficiencies serve to further exacerbate the original underlying metabolic derangements.

The effects of stress deserve special mention since it is a critical mediator of nutrient depletion and CM disease risk as well. Stress is defined as any entity, internal or external, that disrupts normal homeostasis. Integrity of hypothalamic–pituitary–adrenal (HPA) axis function is essential for maintaining homeostasis, and chronic stress can produce maladaptive imbalances in normal HPA function [9–11]. Chronic stress can also lead to an adaptive increase in the production of inflammatory cytokines and oxidative stress [12], both of which exacerbate CM disease risk. Additionally chronic stress also leads to decreased levels of B vitamins, vitamin C, magnesium, chromium and zinc through a variety of mechanisms [13].

Magnesium

Magnesium is an intracellular cofactor responsible for over 300 enzymatic reactions involving protein and nucleic acid synthesis and energy production [14]. Magnesium is essential for insulin activity, decreases platelet aggregation, blocks reuptake of calcium, and is necessary for glucose transport and oxidation [15].

Approximately 75% of Americans have a magnesium intake below the recommended daily allowance (RDA) [16]. Hypomagnesemia is present in up to 65.6% of patients with MeS and 47% of patients with Type 2 diabetes, likely due to underlying insulin abnormalities [17,18]. The risk of developing diabetes increases proportionally to decline in magnesium intake [19]. Several clinical studies have shown magnesium supplementation to be beneficial in reducing blood glucose levels, improving insulin control, and stabilizing the metabolic syndrome cascade [20,21].

Hypomagnesemia has also been associated with cardiovascular diseases such as coronary artery disease and arrhythmias [22], vasospasm [23], sudden death with congestive heart failure [24], hypertension [25], endothelial dysfunction, prothrombotic changes, and acute myocardial infarction [25]. Disease severity, including degree of myocardial tissue damage post-infarction, has been shown to be proportional to magnesium stores, as is the level of hypertension [25]. Low magnesium intake is also associated with an increase in inflammatory markers, such as C-reactive protein (CRP) [26].

Patients with low magnesium states can complain of restless legs, muscle tightness and cramps, heart palpitations, headaches, muscle weakness, and fatigue. Several factors are key in both causing and exacerbating hypomagnesemia. These include poor intake of magnesium rich foods (green leafy vegetables and whole grains) and obesity.

Pharmacologic agents, most notably diuretics, can promote renal magnesium wasting. There is significant interplay between insulin and magnesium, and renal loss of magnesium via hyperinsulinemia has also been shown to occur [27]. Additional evidence supports the role of insulin in impairing intracellular magnesium uptake [28], and low intracellular magnesium levels reduce insulin receptor activity [28].

Chromium

Chromium, a transition metal, is an essential micronutrient required for normal carbohydrate, protein and lipid metabolism. Chromium participates in glucose homeostasis through increasing the phosphorylation of AMP-activated protein kinase (AMPK) and endothelial nitric oxide synthase (eNOS) as well as facilitating the translocation of GLUT4 insulin receptors to the cell membrane [29].

Diets high in simple sugars (comprising more than 35% of calories) can increase chromium excretion in the urine [30]. Infection, intense exercise, pregnancy and lactation, and stressful states (such as physical trauma) increase chromium losses and can lead to deficiency, especially if chromium intakes are already low. There are also reports of significant age-related decreases in the chromium concentrations of hair, sweat, and blood [31].

Low levels of chromium are associated with insulin resistance, elevated blood glucose, high cholesterol and triglycerides, and decreased lean body mass [32]. Chromium deficiencies have been linked to both the development of type 2 diabetes and cardiovascular diseases [33,34]

Average daily intake of chromium for adults is generally lower than recommended, and up to 90% of the US population fails to meet minimum dietary requirements. Stress exacerbates loss of chromium and potentiates age-related decline in absorptive capacity of chromium [31] and can also be depleted by prescription corticosteroid drugs [35].

Vitamin D

Vitamin D is a fat-soluble hormone and in conjunction with parathyroid hormone, is best known for its regulation of calcium and phosphorus metabolism. Vitamin D is produced primarily in the skin from 7-dehydrocholesterol via activation by solar ultraviolet radiation [36]. Additional sources of vitamin D include dietary intake and oral supplementation.

Independent of the source, all vitamin D is converted in the liver to 25(OH) vitamin D, the major circulating form of the vitamin. The kidneys produce the biologically active hormonal form of vitamin D known as 1,25 (OH)2 vitamin D in the final step of vitamin D activation. Vitamin D receptors (VDRs) have been identified in virtually every tissue, including bone, kidney, skeletal, heart, adrenal, stomach, liver, skin, breast, pancreatic, immune, brain, prostate, ovaries, and testes [37].

Vitamin D deficiency has been implicated in a number of chronic diseases including cardi-

ovascular disease, insulin resistance and diabetes (both Type I and 2), auto-immune disorders, cancer, obesity, and osteoporosis. There is substantial literature particularly highlighting the effects of vitamin D on insulin availability and function. Pancreatic β islet cells have both vitamin D receptors (VDR) and vitamin D-dependent calcium binding proteins (CaBP) [38].

In obese patients, vitamin D is selectively stored in body fat thereby making it less bioavailable to engage in such functions as insulin regulation. It is through this mechanism that vitamin D deficiency can promote insulin resistance in obese patients [39]. Vitamin D also has immunomodulatory and anti-inflammatory effects that may indirectly improve insulin sensitivity since inflammation and immune dysregulation are known components of MeS and diabetes [40]. Finally, studies have determined seasonal variations in glycemic control in type 2 diabetics. Vitamin D deficiency induced by limited sun exposure during the winter months may partially explain these findings [41].

Vitamin D also impacts cardiovascular function by directly acting on cardiomyocyte VDRs and by indirectly influencing circulating hormones and calcium [42]. Vitamin D has been implicated in the renin–angiotensin–aldosterone system (RAAS) as a negative regulator [43] and as an immunomodulator of inflammatory cytokines IL-6 and TNFα [44].

In humans, low vitamin D has been strongly linked to hypertension [45], endothelial dysfunction [46], peripheral artery disease [47], atherosclerosis [48], myocardial infarction [49], ischemic stroke [46] and heart failure [50]. In addition, vitamin D insufficiency has been associated with cardiovascular and all-cause mortality [51]. Those with blood levels of vitamin D below 15ng/ml have been shown to have twice the risk of a cardiovascular event such as a heart attack, heart failure or stroke in the next 5 years compared to those with higher levels of vitamin D [52]. A review of studies that included 99,745 participants found that the highest levels of serum 25[OH] vitamin D were associated with a 43% reduction in cardiometabolic disorders [53].

It is estimated that one billion people worldwide have vitamin D deficiency or insufficiency [7]. Age, season, northern latitudes, decreased liver and kidney function, obesity, poor dietary intake, dark skin tone and certain medications (corticosteroids, phenytoin) all contribute to decreased vitamin D levels [54]. Low levels of vitamin D are commonly found in the aging patient, but approximately 50.8 million children/adolescents have a vitamin D insufficiency [55].

Coenzyme Q10

Coenzyme Q10 (CoQ10), a potent antioxidant, is a vitamin-like compound present in virtually all cells with higher concentrations located in the heart, liver, kidney, and pancreas [56]. CoQ10 is a cofactor in the electron transport chain that is involved in cellular respiration and the generation of ATP. Small amounts of this cofactor can be obtained from dietary sources such as meats and seafood [57].

As is true for many cofactors and nutrients, pharmacologic agents are frequently implicated as the causative factor inducing deficiency states. In the case of CoQ10, statin drugs (HMGCoA reductase inhibitors) have been particularly offensive. In patients with statin drug induced myopathies, cellular pathology, such as mitochondrial myopathy and apoptosis, and serological abnormalities, such as elevation in creatine kinase levels, are often lacking. In these patients, depletion of CoQ10 has been implicated in contributing to the underlying etiology of myopathy [58].

Other drugs have also been implicated in lowering CoQ10 levels including thiazide diuretics, beta-blockers, second-generation sulfonylureas, and biguanide medications [59]. Many of these drugs are used simultaneously in patients with CM disease thereby necessitating a thorough understanding of their cumulative effects on nutrient depletion. It has been demonstrated that CoQ10 concentrations can fall by as much as 54% in patients who are on statin drug therapy, and the degree of CoQ10 depletion correlates directly in a dose-dependent fashion [60].

Clinical manifestations of CoQ10 depletion include cardiomyopathy, hypertension, angina, stroke, cardiac dysrrhythmias, insulin resistance, fatigue, leg weakness, decline in immune function and loss of cognitive function [56,61,62]. Ironically, these are the very conditions these pharmacologic agents are utilized to treat.

Drug-Induced Nutrient Depletion in the CM Disease Patient

A significant potential challenge facing the clinician treating patients with CM risks and MeS is the problem of drug-induced nutrient depletions. In the medical management of patients with CM risk factors, several classes of drugs may be employed with the potential for depletion of nutrients. It is these so called drug-induced nutrient depletions that can induce untoward metabolic changes that further exacerbate many aspects of MeS and potentially create new co-morbidities. The principle drugs utilized in the management of a MeS patient can include diuretics, beta-blockers, cholesterol-lowering drugs, oral diabetic agents, and anti-inflammatory drugs. Common side effects and their relative nutrient depletions are listed in Table 1.

Prescription medications used in the treatment for patients with CM disease are among the top selling drugs in the US. Anti-hypertensive agents and cholesterol lowering medications top the list, with prescription sales of $18.4 billion [63]. Yet adverse drug side effects cause 106,000 deaths and hospitalization of over two million people annually and is the fourth to sixth leading cause of death in the US [64].

With increasing evidence that certain prescription medications deplete essential nutrients from the body, it is prudent for the clinician to assess nutrient deficiencies in patients taking prescription medications, particularly those at risk for CM disease. Not all individuals, however, will experience such effects at all, or to the same degree. Multiple factors affect whether, and to what extent, such nutrient depletions will occur. Variations in diet, genetic differences, individual stress, and level of physical activity all contribute to the nutritional status of the individual both prior to and during drug administration. Consequently, individual patient responses to drug therapy may vary and should be monitored and evaluated on a case-by-case basis.

Evaluation and Treatment of Nutrient Deficiencies

Laboratory tests to measure nutrient deficiencies are extremely important to the clinician in assessing and treating the metabolic imbalances in the patient with CM risk factors. Several laboratories now offer complete nutrient profiles, including assessment of CoQ10 levels, tests that may be uncommonly recommended by the practitioner. Table 2 summarizes common nutrient deficiencies found in patients treated for MeS. Examples of diagnostic laboratories include Metametrix Labs of Duluth Georgia, USA (www.metametrix.com) and Genova Diagnostics of Asheville, NC, USA (www.gdxcom).

Magnesium

Although magnesium is an intracellular cation, serum magnesium is generally the only parameter explored. Unfortunately, the reliability of serum magnesium values is unpredictable as an index of total body levels, and even as an indication of abnormal blood levels, unless there is profound deficiency. A more efficient analysis is the red blood cell (RBC) magnesium test. This test reveals the average of the amount of magnesium that has been in cells in the last 4 months. RBC magnesium is the most precise way to assess intracellular magnesium status. Appropriate RBC magnesium levels for adults are 4.0–6.4 mg/dl.

The major dietary sources of magnesium intake include whole grains, legumes, nuts, and green leafy vegetables. Generally, recommended dosages of magnesium (in absorbable form including citrate, glycinate, amino acid chelate, or malate) for repletion of stores are 400–800 mg daily.

Chromium

Chromium supplementation has been reported in clinical trials for over five decades to improve insulin regulation and glucose tolerance in people with type 1 and 2 diabetes mellitus, gestational diabetes, and steroid-induced diabetes [65,66]. Chromium is not found in sufficient amounts in food to replenish tissue stores or to affect clinically significant improvement in blood glucose control [67]. Serum chromium levels in the average adult should range from 0.05–0.5 μg/ml.

Chromium supplementation of 200–800 μg daily is recommended in those at risk for depleted chromium stores. Chromium histidinate is known to be the most absorbable form

Table 2 Commonly depleted nutrients in the patient with metabolic syndrome

Vitamin/mineral (dosage range)	Laboratory testing	Symptoms of deficiency	Depleting factors
Chromium (200–800 μg daily; chromium histidinate more absorbable than picolinate)	Serum chromium level. Adult: 0.05–0.5 μg/ml	Blood sugar imbalances, insulin resistance, diabetes, fatigue, hypertension, obesity, mood disturbances	Diets high in refined carbohydrates; lack of exercise
CoQ10 (50–300 mg daily)	Serum CoQ10 level. Adult: 3–7 μg/ml	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	Medications including ''statins'', biguanide and sulfonylurea hypoglycemics, beta blockers, thiazide diuretics, tricyclics (TCAs), haloperidol, oral contraceptives
Magnesium (400–800 mg daily; use highly absorbable forms including glycinate, amino acid chelate and citrate)	RBC magnesium levels. Adult: 4.0–6.4 mg/dl	Muscle cramps, weakness, fatigue, insomnia, restless leg syndrome, irritability, anxiety, insulin resistance, depression, high blood pressure, cardiovascular problems, headaches	Medications including oral contraceptives, antibiotics including tetracyclines/aminoglcosids, thiazide diuretics,
Vitamin D (400–2000 IU of daily depending upon assessment)	Serum 25–hydroxyvitamin D [25(OH)D]: 35–55ng/ml	Osteoporosis, increased risk of skeletal fractures, hearing difficulties, depression, hormonal imbalances, muscular weakness, hypertension, autoimmune diseases, multiple sclerosis, type 1 diabetes, schizophrenia and decreased immunity	Lack of sunlight, pregnancy and breastfeeding, eating disorders, bariatric surgery, chronic stress, hormonal imbalances, dark skin and vegetarians. Medications including proton pump inhibitors, H2 blockers, orlistat, anticonvulsants (including carbamazepine, phenytoin, primidone), corticosteroids

of chromium. Chromium picolinate, a popular form of chromium supplementation, has been under some scrutiny for its potential to cause cancer. A laboratory animal study found that chromium picolinate may cause chromosomal damage in mice ovarian cell cultures, although blood levels were approximately 50,000 times the normal human levels [68]. Dietary sources of chromium include seafood, oysters, meat, liver, cheese, spinach and broccoli.

Vitamin D

Vitamin D deficiency can result from inadequate dietary intake, insufficient exposure to sunlight (which reduces the body's synthesis of vitamin D), and kidney or liver malfunctions, which inhibit the conversion of vitamin D to its metabolically active forms [69]. Vitamin D does not occur in significant amounts in many foods, but does occur in small and variable amounts in milk, butter, cream, egg yolks, and liver, with milk fortified with vitamin D being the major source of this nutrient in the US. Although $1,25(OH)_2$ is the active form of vitamin D, when testing patients for vitamin D status, $1,25(OH)_2$ vitamin D is a difficult and expensive test and is not an accurate measure of vitamin D status [70]. When patients are vitamin D deficient, the parathyroid hormone increases and drives the renal 1-alpha-hydro-

xylase, so that $1,25(OH)_2$ vitamin D levels increase. Only in severe deficiency, when substrate is depleted, does the $1,25(OH)_2$ vitamin D become low. A blood calcidiol (25-hydroxyvitamin D or 25(OH)D) level is the accepted way to determine vitamin D nutritional status. The optimal level of serum 25-hydroxyvitamin D (25(OH)D) is 35–55 ng/ml (or 90–140 nmol/l).

CoQ10

Humans can display a range of coenzyme Q10 (CoQ10) levels in serum. Unfortunately, high circulating CoQ10 does not indicate sufficient levels for production of ATP in the mitochondrial electron transport chain. CoQ10 depletion from the use of prescription medications commonly used in the MeS patient (such as diuretics, oral hypoglycemics, statins and beta blockers) can interfere with CoQ10 production, compromising cellular energy production and creating more CM risk factors. Clinicians should consider the implications of chronic mild decreases of CoQ10 and its impact on the progression of the metabolic pathology as it relates to the cardiovascular component. Urinary levels of CoQ10 can help determine the antioxidant capacity and serum CoQ10 levels directly measure the levels of this nutrient. Serum levels should be approximately 3–7 μg/ml in the average adult [71].

There is preliminary evidence suggesting that CoQ10 supplementation in conjunction with statin drugs may reduce the incidence of myopathy but results of clinical trials have been mixed. Several studies have demonstrated reduced pain intensity in patients on statin drugs by simultaneously administering 100 mg of CoQ10 daily compared to placebo [72–74]. Other trials have found there to be no benefit in such patients even when patients are treated with doses up to 200 mg. Clearly, one reason for the differences in these findings may be demographics of the patient populations used in these trials. Given the substantial use of statin drugs in patients, further study on the clinical efficacy of CoQ10 in such patients is warranted.

The value of CoQ10 in hypertension was demonstrated in a meta-anlaysis performed on 12 clinical trials evaluating its effects on hypertension. CoQ10 was concluded to lower systolic blood pressure by up to 17 mmHg and diastolic blood pressure by up to 10 mm Hg without significant side effects [75]. In another trial, supplementation of CoQ10 enabled hypertensive patients to reduce their medications. A mean dose of 225 mg in 109 patients led to discontinuation of 1–3 medications in 51% of patients within 6 months (average time 4.4 months), 80% of the individuals had been diagnosed for 9.2 years. Only 3% of subjects required the addition of one more drug [76].

In subjects treated with CoQ10, muscle fibers were examined in an elderly population preparing for hip surgery. Treated individuals had a lower proportion of type 1 (slow twitch) fibers and a higher concentration of type IIb (fast twitch) fibers compared to age matched placebo-treated patients. This shift is consistent with fiber composition found in younger populations [77] associated with a significant change in gene expression of proteins encoding muscle fiber composition. The protective and regenerative effects of CoQ10 on skeletal muscle are promising and it may be theorized that low CoQ10 status could accelerate aging and genetic changes in muscle tissue. The recommended clinical dosage range for repletion of CoQ10 varies from 50–300 mg per day.

Case Resolution

The patient underwent an extensive metabolic evaluation to clarify both his nutritional status and the pattern of hormonal abnormalities that might be contributing to his MeS. The patient was open to investigating which nutrients were deficient, and how to replace them appropriately.

Laboratory results included the following:

- RBC magnesium: 2.5 mg/dl (4.0–6.4 mg/dl)
- Chromium: 0.06 μg/dl (0.05–0.5 μg/ml)
- Coenzyme: Q10 0.2 μg/dl (3–7 μg/ml)
- 25 (OH) vitamin D: 7 (35–55 ng/ml).
- Fasting insulin: 36 uU/ml (5–25 uU/ml)
- Total testosterone: 150 ng/dl (270–1070 ng/dl)
- 4-point salivary cortisol test demonstrated a flattened slope with associated hypocortisolism.

The patient's overall combined nutritional and hormonal profile indicated significant nutrient depletions alongside hyperinsulin-

Table 3 Comparative laboratory results

	Initial visit	3 month follow up visit
Blood pressure	138/89	121/82
Fasting glucose	110 mg/dl	92 mg/dl
Fasting insulin	36 uU/ml	6 uU/ml
Total cholesterol	235 mg/dl	203 mg/dl
LDL	160 mg/dl	98 mg/dl
HDL	39 mg/dl	55 mg/dl
Triglycerides	179 mg/dl	106 mg/dl
RBC magnesium	2.5 mg/dl	4.5 mg/dl
25 (OH) vitamin D	7 ng/ml	55 ng/ml
Total testosterone	150 ng/dl	15 ng/dl

emia, hypogonadism, and hypothalamic–pituitary–adrenal dysregulation. A program of specific nutrient repletion was instituted that included magnesium glycinate 300 mg twice daily (glycinate is a highly absorbable form with less diarrheal side effects than the more common oxide form), chromium GTF 500 μg twice daily, and coenzyme Q10 200 mg daily. Vitamin D2 50,000 Units was given once weekly for 4 weeks, then levels were rechecked. His vitamin D level increased to 45 ng/ml, and he was switched to vitamin D3 2000 IU daily for maintenance dosing. A low glycemic index diet was initiated as well.

The patient also elected testosterone replacement therapy in addition to instituting stress reduction techniques and herbal supplements to improve his physiologic stress response. A 1% 5-gram testosterone patch, and rhodiola 125 mg twice daily (standardized to 5% rosavins) were advised as initial treatment. *Rhodiola*, a popular adaptogenic herb used in Asian and European traditional medicine, is capable of inhibiting excess cortisol response due to stress, and has demonstrated effective anti-fatigue and anti-depressant qualities [78]. It is used routinely to treat HPA dysfunction and induce a normal cortisol response. L-theanine 200 mg three times per day was recommended as well. L-theanine, an amino acid found in the tea plant *Camellia sinensis*, blocks the major excitatory brain neurotransmitter L-glutamate, improves mental alertness and feelings of relaxation simultaneously [79], and induces alpha-brain wave activity, which is associated with meditative states [80,81]. The patient returned to clinic after 3 months to review progress and laboratory results. He had lost 15 pounds, reported increased energy levels, and complete elimination of joint aches. His comparative laboratory results are shown in Table 3.

The patient chose not to re-measure chromium or coenzyme Q10 levels due to the out-of-pocket expense ($150). He is now more committed to managing his health, and has been able to initiate a walking exercise program utilizing a pedometer (10,000 steps daily). He will return to clinic in another 3 months for review of progress.

Conflict of interest

The authors have no conflicts of interest to report.

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