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HIDDEN DISRUPTIONS IN METABOLIC SYNDROME: DRUG-INDUCED NUTRIENT DEPLETION AS A PATHWAY TO ACCELERATED PATHOPHYSIOLOGY OF METABOLIC SYNDROME

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STATEMENT OF PURPOSE
In medicine today, the management of various co-morbid conditions and disorders is a complex relationship between the metabolic disruption of the condition, the nutrient status of the individual, the interaction of drug therapies, genetic individuality, and environmental and lifestyle influences. Metabolic syndrome is a primary example of a condition with these very complex relationships. As drug therapy is managed as a first line of defense in the treatment of metabolic syndrome, it is important to evaluate the underlying nutrient depletions that may occur and their metabolic consequences in order to prevent progression to the very diseases we are trying to prevent.

TARGET AUDIENCE
This activity is designed to meet the educational needs of physicians and other healthcare professionals who diagnose, treat, and manage patients who have or are at risk for metabolic syndrome.

OBJECTIVES
After completing this article, participants should be able to:
1. Identify potential nutrient depletions of drugs that are commonly used in metabolic syndrome.
2. Understand the potential implications of long-term nutrient depletion on cellular metabolism.
3. Describe conditions or diseases that can result from drug-induced nutrient depletion.
4. Explain the essential need for vitamins and minerals in homeostatic physiology. (*Altern Ther Health Med*. 2006;12(2):26-33.)

DISCLOSURE
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One of the potential challenges facing healthcare professionals today is the problem of drug-induced disease. With polypharmacy prescribing occurring in younger and younger populations, it is becoming increasingly important to assess nutrient depletion risks as they relate to future symptoms, conditions, or progression of disease.

One of the most significant issues facing healthcare in the United States today is the epidemic of individuals with diagnosed obesity, diabetes, and cardiovascular disease or who are exhibiting

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an increased risk of developing any combination of the 3. Combinations of prediabetic conditions such as elevated blood glucose or fasting insulin levels combined with at-risk lipid profiles, increased blood pressure, and increased waist:hip ratios have been labeled *metabolic syndrome* or *Syndrome X*. Members of the medical community are debating whether this syndrome should exist as its own diagnosis or it is simply a cluster of co-morbid symptoms that are presenting in the population.[1] Regardless, the risks to individuals displaying these clusters of symptoms are very real, even if the terminology or classification of the symptoms as a syndrome is yet to be determined. For simplicity, we will refer to the cluster of symptoms as metabolic syndrome, which undeniably is an epidemic in the United States. The American Heart Association estimates that more than 50 million Americans exhibit the constellation of symptoms of metabolic syndrome.[2]

In the medical management of these individuals, several classes of drugs may be used, and some have the potential to cause nutrient depletions that could induce metabolic changes that further the progression of any component of metabolic syndrome or create new morbidities. The principle drugs used to manage patients with metabolic syndrome include diuretics, beta blockers, cholesterol-lowering medications, anti-diabetic medications, and agents for management of obesity.

Several factors should be noted before discussing the relative impact of drug-induced nutrient depletion. Whether a nutrient depletion will occur is a complex and multi-factorial issue. Variations in diet, genetic differences, and individual stress and activity levels all contribute to the nutritional status of the individual before drug therapy is administered. Therefore, responses to drug therapy are highly individualized.

A typical presentation of a patient with metabolic syndrome is as follows: a 30-year-old, obese, black male with a body mass index (BMI) of 30 presents with a waist circumference of 42 inches. His blood pressure is 138/89, fasting blood glucose is 110, fasting insulin is 17; he has elevated high-sensitivity C-reactive protein (HS-CRP), a total cholesterol of 235 (low-density lipoprotein [LDL] 160, high-density lipoprotein [HDL] 39), and a triglyceride level of 174. His comprehensive metabolic panel is otherwise unremarkable. Although he has been encouraged at previous visits to change his diet and exercise, he has failed to do so. He has a family history of heart disease and complains of joint aches, for which he takes ibuprofen as needed. Because of noncompliance with lifestyle and dietary changes, drug intervention is necessary.

According to the current guidelines for management of metabolic syndrome, this patient could potentially be started on any or all of the drugs listed in Table 1.[3] In practice, patients come in with one or any combination of these lab values and clinical presentations, indicating the need for one or more of these drugs.

DISCUSSION OF SIGNIFICANT NUTRIENTS DEPLETED

Rather than discuss the individual drugs listed in Table 1, let's review the principle nutrients depleted and their relationship to metabolic syndrome, insulin resistance, cardiovascular disease and the associated risks. Because these are chronic conditions, the drugs are used long-term, and patients are on several of these medications for many years. It is important to remember that metabolic disturbances build over time with subtle disturbances in enzyme function, leading to an avalanche of metabolic disruption. Often, patients are displaying symptoms of a nutrient depletion, and rather than a nutrient being given, other drugs are being prescribed to mask metabolic problems that have been brought about by drug therapy. Pharmacists are increasingly being called upon not only to streamline pharmaceutical use in patients, they are being asked to participate in the management of diabetes and lipid management as well as other conditions.[4] Part of this management is assessing the overall nutritional status of the patient. In assessing individuals for possible drug-induced nutrient depletions, the prescribed medications may have no known nutrient depletions, but signs and symptoms of nutrient deficiencies should always be assessed regardless, because many lifestyle factors, such as smoking and drinking, can contribute to nutrient depletions. Addressing nutritional deficiencies is not only a foundation to good healthcare, but in a healthcare environment where prevention is increasingly being mandated because of out-of-control healthcare costs, it is also a cost-effective way to improve the overall health and well-being of the patient and prevent further co-morbidities.

Magnesium

One of the most significant nutrients depleted from first-line drug therapy for hypertension is magnesium.[5] In pharmacy practice, when patients are given thiazide diuretics for blood pressure, typically only potassium depletion is addressed. Patients are advised to drink orange juice or eat a banana, which are rich sources of potassium. Often, no education is given regarding the potential for magnesium depletion, despite the fact that many listed side effects of thiazide diuretics are also signs and symptoms of magnesium depletion. The literature on this topic is controversial,[6] but enough studies have shown a magnesium-depleting effect from thiazides to at least justify a screening for magnesium depletion symptoms among thiazide users. This is especially true when we consider that the clinical manifestations of hypomagnesaemia can be quite severe.

Magnesium is involved in more than 300 enzymatic reactions in the body. It is needed for proper nerve transmission, energy production, muscular activity, temperature regulation, cell detoxification, blood pressure regulation, and vasospasm regulation, and it helps build healthy bones and teeth. Magnesium deficiency is associated with increased incidence of atherosclerosis, hypertension, stroke, and heart attack. Magnesium plays a role in inhibiting platelet aggregation, blood thinning, blocking calcium reuptake, relaxing blood vessels, and increasing oxygenation of the heart by improving contractility.

Approximately 75% of Americans' intake of magnesium is below the recommended daily allowance (RDA) to begin with.[7] In addition, many lifestyle factors, including stress and drinking alcohol, can deplete magnesium, so it is easy to understand how, with the addition of drug therapy, a clinically significant low magnesium level can occur. It should be mentioned that serum magnesium is a poor measure of magnesium status because homeostatic

TABLE 1 Drugs That Are Commonly Used in Metabolic Syndrome and That Cause Nutrient Depletions[8,9]

Drug	Potential nutrient loss	Potential health consequences
Thiazide diuretics: hydrochlorthiazide, chlorthiazide, indapamide, metolazone, and combination drugs containing these agents	Coenzyme Q10 (CoQ10) Magnesium Potassium Sodium Zinc	Cardiovascular problems, immune weakness, low energy, muscle weakness, blood sugar dysregulation, palpitation, anxiety, cramps, restless limbs, nervousness, irregular heartbeat, numbness or tingling in the limbs, tinnitus, migraines, insomnia, fatigue, edema, dehydration, memory, slow wound healing, loss of sense of smell and taste, sexual dysfunction
Potassium-sparing diuretics: triamterene and combinations containing this agent	Calcium Folic acid Zinc	Osteoporosis, heart and blood-pressure irregularities, tooth decay, anemia, birth defects, depression, cervical dysplasia, poor wound healing, sexual dysfunction, loss of sense and smell
HMG-CoA reductase inhibitors atorvastatin, fluvastatin, lovostatin, lovostatin, rosuvastatin calcium, pravastatain, simvastatin and combinations containing these agents	CoQ10	Cardiovascular problems, weakened immunity, muscle weakness, low energy, blood-sugar regulation
Anti-diabetic drugs		
Metformin	B12 Folic Acid CoQ10 B6	Anemia, tiredness, fatigue, weakness, increased cardiovascular risk, depression, parathesia, birth defects, cervical dysplasia, increased cancer risk, muscle weakness, blood-sugar dysregulation, weakened immunity
Sulfonylureas Second-generation	CoQ10	Cardiovascular problems, weakened immunity, low energy, muscle weakness, blood-sugar dysregulation
ACE inhibitors: captopril, enilapril, fosinapril, lisnopril, quinapril, ramipril, trandolapril	Sodium Zinc	Fatigue, dizziness; documented only in captopril and enalapril: lowered immunity, slow wound healing, loss of senses of smell and taste, sexual dysfunction
Beta blockers: propranolol, sotolol, nadolol, atenolol, acebutolol, metaprolol, timolol, pindolol	CoQ10 Melatonin	Cardiovascular problems, weakened immunity, low energy, muscle weakness, blood sugar dysregulation, insomnia
Thiazolidinediones	None known	
Angiotensin receptor blockade drugs	None known	

HMG-CoA=3-hydroxy-3-methyl-glutaryl-CoA
ACE=angiotensin-converting enzyme

mechanisms keep blood levels fairly constant by pulling magnesium from bone and other body tissues. It has been suggested that red blood cell levels are a more reliable indicator of magnesium status.[10] Some researchers contend that mid-normal magnesium levels could indicate an intracellular depletion, however. Likewise, levels do not always correspond with utilization in the body.

Symptoms of magnesium deficiency include the following.

- Muscle cramps and spasms, vasomotor spasms
- Anxiousness, nervousness, insomnia
- Increased blood pressure
- Blood-sugar dysregulation
- Depression
- Fatigue
- Arrhythmias, palpitation, irregular heartbeat
- Migraines
- Constipation
- Osteoporosis
- Kidney stones

Manifestations of Magnesium Deficiency

Even marginal magnesium deficiency can decrease myocardial magnesium, which can directly affect contractility and excitability of the heart. The mechanism of action of this result is primarily by the reduced regulation of calcium ion channel. Even perfusion of the heart is compromised. Studies have reported that low magnesium can lead to coronary vasospasm, reduced energy metabolism, changes in potassium homeostasis, and excessive induction of free-radical generation.[11,12] In another study demonstrating this principle, a diet low in magnesium and high in sucrose progressively induced elevations in triglycerides and a reduction of insulin binding to erythrocyte insulin receptors (increased insulin resistance) over a 3-month period in an animal model.[13]

Many of the symptoms and conditions that develop, progress, and are prescribed for in metabolic syndrome mimic the symptoms of magnesium depletion—primarily blood-pressure regulation and blood-sugar regulation. It should be noted that several of the listed side effects of thiazide diuretics are also symptoms of magnesium depletion (eg, irregular heartbeat; low back pain; mood changes; muscle pain, weakness, or cramps; constipation; headache; unusual tiredness or weakness).[14]

An established potential consequence of long-term use of thiazide diuretics is development of type II diabetes, and because of

this, their use is controversial.[15] The medical literature is clearly establishing the role of magnesium in not only insulin regulation, but in inflammatory chemistry.[16] Drug-induced intracellular depletion of magnesium could be playing a significant role in the rapid induction into the complications of metabolic syndrome. A clinical repletion dosage of magnesium of 300-800 mg/day may induce loose stool, so titrate to larger doses if needed.[17]

Coenzyme Q10

One of the most frequently discussed depletions in drug-induced nutrient depletion is the area of CoQ10 depletion and the use of statin medications (ie, 3-hydroxy-3-methyl-glutaryl-CoA [HMG-CoA] reductase inhibitors). This depletion can also occur with the use of diuretics, beta-blockers, and second-generation sulfonylureas and biguanide drug therapies. Cellular CoQ10 levels can be depleted with the use of these drugs. It has been demonstrated that CoQ10 concentrations can decrease by as much as 54% in patients who are on HMG-CoA reductase inhibitor therapy. This has shown a dose-dependent drop in some patient populations.

CoQ10 is a cofactor in the electron transport chain, which is involved in cellular respiration and the generation of adenosine triphosphate (ATP). CoQ10 also is an antioxidant and a principle gene regulator in muscle tissue, playing a key role in tissue metabolism. Clinical manifestations of CoQ10 depletion can include cardiomyopathy, hypertension, angina, stroke, cardiac dysrrhythmias, fatigue, leg weakness, a decline in immune function, and loss of cognitive function.

In one study, muscle fibers in an elderly population preparing for hip surgery were examined. The study showed that CoQ10-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.[18] In this study, significant change in gene expression of proteins was noted. So the protective and regenerative effects of CoQ10 on skeletal muscle is promising and it may be theorized that CoQ10 deficiency could accelerate genetic changes in and aging of muscle tissue.

Another area of clinical concern in patients with metabolic syndrome is the increased risk for Alzheimer's disease. The combination of disruption in mitochondrial ATP and an increase in hydrogen peroxide is one mechanism by which amyloid beta-peptide toxicity can take place. Disruptions in both glucose metabolism and increased free-radical damage have been implicated in the development of Alzheimer's disease. In a promising study, isolated brain mitochondria from diabetic rats were treated with CoQ10. Treatment with CoQ10 attenuated the decreased oxidative phosphorylation efficiency and halted the hydrogen peroxide production induced by neurotoxic peptides. This indicates that CoQ10 treatment changed the mitochondrial alterations in the amyloid beta 1-40, suggesting it could play a role in altering the cellular energy deficits associated with diabetes and the progression of Alzheimer's.[19] These findings suggest that it does not make sense to administer drugs that deplete CoQ10 without repletion when mitochondrial energy deficits clearly are involved in progression to Alzheimer's disease.

The value of CoQ10 in hypertension was demonstrated in a clinical trial in which supplementing CoQ10 decreased systolic and diastolic blood pressure, decreased total cholesterol, and increased HDL cholesterol.[20] 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% required the addition of 1 drug.[21] Another study found that drug-related myopathy, which is a complaint of CoQ10 therapy, was shown to be associated with a mild decrease in CoQ10 without presenting a histochemical or mitochondrial myopathy or even morphologic evidence of apoptosis in most patients examined. The net meaning of this is that significant cellular pathology may not exist, and yet symptom expression could be likely.[22] So even though there may be no evidence of changes via creatine kinase concentrations, metabolic disruption of ATP production and cellular energetics is probable.

Given that several of the most common drugs used in metabolic syndrome deplete CoQ10, clinicians should consider the implications of chronic mild decreases of CoQ10 and their impact on the progression of metabolic pathology. The recommended clinical dosage for repletion of CoQ10 is 30-300 mg per day.[17]

Conditions and symptoms associated with CoQ10 depletion include the following.

- Hypertension
- Angina
- Mitral valve prolapse
- Stroke
- Arrhythmias
- Cardiomyopathy
- Poor insulin production
- Low energy
- Gingivitis
- Weakened immunity
- Muscle weakness

Zinc

Marginal zinc deficiencies are thought to be common in the United States. Because of zinc's involvement in more than 300 enzymatic reactions, the symptoms of deficiency can present themselves in a wide array of physiologic dysfunction.

Conditions and diseases associated with zinc deficiency include the following.

- Loss of taste and smell
- Poor wound healing
- Anorexia
- Alterations in immunity including cytokine and killer T cell function
- Depression
- Photophobia
- Night blindness
- Frequent infections
- Disorders of skin, hair, and nails
- Joint pain
- Alteration in hormones including leptin, thyroid, and insulin
- Kidney disease
- Celiac sprue and inflammatory bowel disorders
- Malignant melanoma
- Alcoholism
- Macular degeneration
- Prostate disorders

Zinc is depleted by several of the drugs listed in Table 1. One of the more significant findings related to zinc deficiency is the influence on messenger ribonucleic acid (mRNA) and levels of cytokines

on cell lines. Zinc deficiency decreased expression of interleukin (IL)-2 and interferon (IFN)-γ in the T_H1 cell gene expression, and tumor necrosis factor (TNF)-α, IL-1β, and IL-8 gene expression were upregulated.[23] This study clearly demonstrated the effects of zinc on genetic expression of cytokines and that the expression was specific to immune cells. Extrapolated to humans, this would mean that zinc deficiency could increase the production of TNF-α, IL-1β, and IL-8, which is associated with the development of metabolic syndrome,[24] cancer, and Alzheimer's Disease. In addition, it has been shown that increased TNF-α induces insulin resistance and increased oxidative stress.[25] Alterations in TNF-α have been associated with decreased HDL, increased LDL and triglycerides, and increases in C reactive protein. As insulin resistance is increased by diet, mineral deficiencies (eg, magnesium, chromium), stress, lack of exercise, or other factors, the increase in adipocyte-driven TNF-α expression could be exacerbated by zinc-deficient chemistry. The recommended clinical dosage for repletion of zinc is 10-50 mg/day.[17]

Vitamin B_{12} and Folic Acid

For the sake of this discussion, we are going to deal with these 2 nutrients together. The value of B_{12} for reduction of anemia and regulation of DNA and neurologic changes has been established, but there are specific issues that relate to the depletion of B_{12} and the progression of metabolic syndrome in individuals that must be addressed.

Metformin depletes vitamin B_{12} and folate. Metformin is sometimes used in metabolic syndrome to prevent progression to Type II diabetes mellitus and hypertension.[26,27]

Depletion of folate and B_{12} can elevate homocysteine levels. In a trial published in the *European Journal of Endocrinology*, folate and B_{12} therapy was shown to reduce homocysteine levels, ameliorate insulin resistance, and help to resolve endothelial dysfunction in patients with metabolic syndrome. In the treatment group, 5 mg of folate and 500 mg/day of B_{12} for 1 month led to striking results: a decrease in homocysteine of 27.8%, a significant decrease in insulin levels, and an improvement in endothelial dysfunction as evidenced by hyperemic vasodilatation of 29.8% and a decrease in dimethylarginine levels of 21.7%.28 Plasma homocysteine is clearly elevated and is used as a bio-marker in metabolic syndrome. It is also an independent marker for the development of atherosclerotic disease. It is thought that folic acid facilitates and restores endothelial nitric oxide by acting as hydrogen and an electron donor to tetrahydrobiopterin and through the lowering of total homocysteine along with B_{12} by the enhancement of remethylation.[29]

Homocysteine, IL-6, and C-reactive protein can express more dramatically in a C677T mutation of methylenetetrahydrofolate reductase [MTHFR] gene, showing that innate immunity is involved in the pathogenesis of arteriosclerosis in patients with diabetes mellitus who are genetically predisposed.[30] Depletion of folic acid resulting from drug therapy in an individual with the C677T mutation could accelerate the cascade of elevated homocysteine, increased IL-6, and increased C peptide that is associated with metabolic syndrome, cardiovascular disease, and diabetes. In these individuals who are homozygous for the TT genotype of C677T MTHFR, supplementation with 5-MTHF may be necessary to overcome the genotypic barrier for absorption of folic acid.

Depression is a common co-morbidity in heart disease. It may not be as well known that depression in metabolic syndrome is also common.[31] Studies are finding that low folate levels, low B_{12}, and elevated homocysteine levels are correlates in depression.[32,33]

Folate and B_{12} status should be evaluated in patients with metabolic syndrome as it relates to progression of elevated homocystine and depressive symptoms. The recommended clinical dosage to replete folate is 400-800 μg/day, and clinical intervention dosages for severe deficiencies and cervical dysplasia are 1-10 mg/day.[17] Dosage to replete B_{12} is 100-2,000 μg/day, and the most effective route of administration is intramuscular injection.[17]

Conditions associated with folic acid depletion include the following.

- Elevated homocysteine
- Depression
- Cervical dysplasia
- Breast and colon cancer
- Anemia
- Fatigue
- Cardiovascular disease
- Birth defects

Melatonin

On initial inspection, the depletion of melatonin may not seem to have a tremendous impact on metabolic syndrome. But on further inspection, it has been found that chronic depletion of melatonin can directly influence daily rhythm of glucose, reduction in glucose transporter 4 (the insulin-sensitive glucose transporter) levels, and suppression of insulin secretion.[34] The correlation may be that melatonin deficits lead to disrupted sleep, and disrupted sleep can lead to increased insulin resistance. Melatonin also has significant antioxidant effects as it stimulates glutathione peroxidase, superoxide dismutase and catalase, as well as nitric oxide synthases. Melatonin is reported to reduce oxidative stress in diabetic populations.

An evaluation of the National Health and Nutrition Examination Survey revealed that people who slept 5 hours per night had a 73% increased risk of becoming obese vs those who slept 7-9 hours per night.[35] Trials conducted at Stanford University found that people who slept an average of less than 5 hours per night had a 15.5% decrease in leptin, an increase of 14.9% of ghrelin, and a higher BMI, regardless of the exercise and diet habits of the participants.[36] So with loss of sleep, the net effect was that appetite centers were upregulated, BMI increased, and there was a shift in metabolic dysfunction toward metabolic syndrome. When melatonin levels are low, rapid-eye-movement (REM) sleep cycles are disturbed, leading to increased wakefulness throughout the night, and studies have shown that administering melatonin in the late evening hours was significantly more effective than placebo at increasing REM sleep.[37,38]

Under conditions of high stress, cortisol levels increase, leading to a state of hyperarousal. Studies are showing that disturbed sleep as a result of hyperarousal can lead to its own effects on metabolic function (increased TNF-α, increased IL-6, increased visceral fat storage, increased insulin resistance, etc).[39] Other nutrient depletions, such as reduced magnesium status and low folate status (decreased serotonin synthesis) can be simultaneously acting on the sleep center and inducing hyper-arousal. All of this adds up to an increased risk for obesity, diabetes, and cardiovascular disease.

Melatonin may enhance insulin-receptor kinase and insulin receptor substrate-1 phosphorylation, which may improve insulin signaling and may actually counteract TNF-a-induced insulin resistance in Type 2 and metabolic syndrome populations.[40] Lastly, melatonin seems to have a direct effect on inhibiting tumorigenesis. Melatonin helps to inhibit cellular proliferation, stimulated differentiation, and apoptosis.[41] This is particularly interesting, as people with insulin resistance and sleep disturbances are more prone to cancer due to elevations of insulin-like growth factor 1 and increases in the immunologic shift toward chronic inflammatory chemistry, leading to reduced activity of natural killer cells.

Melatonin can be depleted by the use of beta blockers. Because of its potential to disrupt sleep and lead to further problems such as increased appetite, weight gain, insulin resistance, and increased inflammatory chemistry, it is important to assess melatonin levels and administer melatonin if disrupted sleep is present.[17] Cortisol levels should also be evaluated to determine if steps may be necessary to down-regulate cortisol to further address hyperarousal as an underlying cause of insomnia.

CONCLUSION

Nutrient depletions from many drug therapies used in metabolic syndrome can have a profound effect on its progression and the development of new co-morbidities. For example, a patient might start out on hydrochlorothiazide, become insulin-resistant, and then be put on metformin while you begin treating them with statin drugs for lipid abnormalities. As the years pass, complaints of poor sleep, muscle weakness, fatigue, depression, restless motor syndrome, and a host of others are arising. Dysregulation of metabolic pathways should always be evaluated to see if nutrient depletions could be an underlying cause of common co-morbidities such as restless legs, insomnia, low energy, and depression—if for no other reason than to prevent the need for more medications. Because many of the marginal deficiencies do not show up on traditional laboratory tests, patients are often left with no solution—or with another prescription to fill. Nutrients in the form of vitamins, minerals, and other nutraceuticals are relatively inexpensive and offer significant margins of safety. They offer not only a solution to many of the co-morbidities, but used properly, they also can reduce further progression of illness.

Vitamins, minerals, amino acids, and essential fatty acids are needed by every cell of the body to function. With depletion or genetic variation, metabolic consequences could lead to the initiation of chronic illness. Modern drug therapy and the emerging science of natural therapeutics together provide an integrative approach to managing chronic diseases as well as the best approach for disease prevention and wellness.

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