Metabolic Correction: A Functional Biochemical Mechanism against Disease • Part 1: Concept and Historical Background

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Human physiology depends on countless biochemical reactions, numerous of which are co-dependent and interrelated. The speed and level of completion of reactions usually depend on the availability of precursors and enzymes. The enzymatic activity depends on the bioavailability of micronutrient cofactors such as vitamins and minerals. In order to achieve a healthy physiological state, the organism requires that biochemical reactions occur at a controlled rate. To achieve this state it is required that metabolic reactions reach what can be considered an optimal metabolic equilibrium. A combination of genetic makeup, dietary patterns, trauma, disease, toxins, medications, and environmental stressors can elevate the demand for the nutrients needed to reach this optimal metabolic equilibrium. In this, part 1, the general concept of metabolic correction is presented with an elaboration explaining how this concept is increasing in importance as we become aware of the presence of genetic variants that affect enzymatic reactions causing metabolic disturbances that themselves favor or promote the disease state. In addition, part 1 reviews how prominent scientists have contributed in fundamental ways to our understanding of the importance of micronutrients in health and disease and in the development of the metabolic correction concept. [*P R Health Sci J 2015;34:3-8*]

Key words: Metabolic correction, Chronic disease, Genetotrophic disease, Biochemical individuality, Nutrient insufficiency, Functional medicine, Orthomolecular medicine

Nutrition, Metabolism, and Physiological function

Normal metabolic activities require over 40 vitamins and micronutrients (1), in addition to fat (omega-3 and omega-6), protein (8 essential amino acids), and carbohydrates (2). Similarly, other nutrients, such as Coenzyme Q10, acetyl L-carnitine, and lipoic acid, are vital for adequate physiological function (3). Many metabolic reactions require these micronutrients for their completion.

The ideal amount of every nutrient will facilitate maximal physiological functionality. An insufficiency or deficiency may interfere with a biochemical pathway that leads to imbalances or physiological derangements that require adaptation and commonly leads to disease. Such adaptation means that while many partially depleted individuals do not function at 100% efficiency, they nevertheless do not present with any signs of apparent disease or symptoms in the short term. However, the chronic effects are difficult to study and may be involved in common degenerative conditions. A leading hypothesis is that a person supplied with the optimum nutrition will acquire

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disease immunity and an improved physiology. In the past, this hypothesis has been highly useful when applied to the task of reducing human illness, an example of its usefulness is the identification of the nutritional deficit that causes the previously common disease pellagra. Assuming that all such nutritional illnesses have been discovered is unwarranted. The optimal concentration of nutrients needed by different individuals may vary even for a single subject. Certain individuals have a greater need for specific nutrients. Moreover, individuals' needs may vary substantially according to their specific physiological requirements (4, 5). Variations in individual micronutrient needs can be caused by low dietary ingestion of micronutrients, poor digestion, food sensitivities, defective metabolic enzymes, the excessive formation of metabolic intermediaries, or any combination of two or more of the previous (1).

Many health professionals do not recognize the wide range of important metabolic functions of vitamins, minerals, and other nutrients at the cellular level as cofactors for enzyme activity in biochemical reactions. The importance of micronutrients to the human metabolism and to biosystem control has not been completely elucidated, partly because of the complexity of cellular-physiological systems. Vitamins such as B-complex and metals such as zinc, copper, manganese, and selenium often are integral parts of the functional molecular structure. This is why many enzymes require these nutrients for their proper functioning (6). Enzymes play a crucial role in regulating and coordinating the myriad biochemical reactions necessary in living organisms.

Metabolic nutrition is commonly recognized as the study of how diet and nutrition affect the body's physiology. Nutrition, in general, is a complex interdisciplinary science, and its importance is central to the maintenance of good health. Not including starvation and overeating that are both prevalent in Western societies, nutrition can also be classified into 3 levels: *poor*, *fair*, and *good*. Signs of poor nutrition include severe underdevelopment (usually seen in children) and such deficiency illnesses as scurvy, beriberi, pellagra, rickets, and kwashiorkor, among others (1). Fair nutrition is good enough to prevent well-defined deficiencies but not good enough to promote good health and proper development. This second-rate nutrition is, unfortunately, the kind which we have become accustomed to accepting in a world full of junk food and is often regarded as satisfactory (7). Good nutrition supplies an adequate amount of energy for the body's needs, in addition to providing necessary amounts of high quality macronutrients (protein, carbohydrates, and fats) and micronutrients (vitamins, minerals, and other cofactors). Originally the concept of a balanced diet was developed to prevent deficiency diseases, which development was based on the knowledge that appropriate food items would provide the minimum required nutrients needed by the body. A balanced diet is an approximation of what might be called the "ideal" diet, and it appears to provide sufficient nutrition in the short term, according to current knowledge. This so-called good nutrition may be insufficient to provide physiological optimization and lead to an excellent state of health. Importantly, a current hypothesis is that food by itself may not provide sufficient vitamins and micronutrients for preventing deficiency/insufficiency (8).

In practical terms, the insufficient dietary intake of vitamins and minerals is common and is typified by the excessive ingestion of calorie-rich, low in micronutrients, refined food (1). Caloric excess frequently occurs with the insufficient intake of micronutrients, and this phenomenon is known as *Hidden Hunger* (9). These nutrient insufficiencies may produce metabolic disruptions (10) and may, in addition, increase the risk of chronic disease. Occasional scarcities of micronutrients have been prevalent during the evolution of the human species due to the changes in environmental conditions that have occurred over time. Natural selection favors short-term (emergency) survival at the cost of long-term health (10). During life-threatening situations, short-term survival was (and still is) ensured by allocating already scarce micronutrients to such vital functions as vision, respiration, and muscle contraction (10). As micronutrients become scarce, an adaptive mechanism for allocating scarce micronutrients is activated. This mechanism, which performs a kind of triage in the undernourished body, is responsible for prioritizing how the aforementioned scarce nutrients are to be used, generally reserving them for the most fundamental life-preserving functions. At this point, the long-term survival of the organism—the individual—is not a preeminent concern. This mechanism, which performs a kind of triage in the undernourished body, is responsible for prioritizing how the aforementioned scarce nutrients are to be used, generally reserving them for the most fundamental life-preserving functions. At this point, the long-term survival of the organism—the individual—is not a preeminent concern. One example of how triage works is that the metabolic reactions of enzymes involved in ATP synthesis have a higher priority than DNA repair enzymes do, as these reactions also do over both the production of complex neurological chemicals and the production of immune system components (cellular and humoral). The degree of adaptation is limited, and negative metabolic repercussions arise. One such repercussion is the accumulation of homocysteine, a non-protein α-amino acid, the levels of which increase when vitamin B is in short supply; elevated homocysteine levels are associated with increased risks to cardiovascular and neurological health.. Nutrient depletion disturbs normal biochemical controls and the healthy physiological equilibrium, potentially favoring a state conducent to chronic disease (1, 5). Since vitamins such as folic acid and pyridoxine require metabolic processes for their activation, the presence of certain genetic variants (polymorphisms) with defective enzymes may hinder this activation and therefore contribute to the accumulation of

toxic metabolites such as the previously mentioned homocysteine.

Homocysteine (Hcy) is considered a potentially toxic amino acid and a risk factor for inflammation, cardiovascular disease, stroke, blood clot formation, dementia, and Alzheimer's disease, among other degenerative diseases (12–17). It is postulated that the methylation of Hcy to methionine could result in the reduction of the number of adverse cardiovascular events, strokes, and vascular thromboembolisms as well as the diminishment of such conditions as peripheral neuropathy, dementia, and Alzheimer's disease the reduction of the number of adverse cardiovascular events, strokes, and vascular thromboembolisms as well as the diminishment of such conditions as peripheral neuropathy, dementia, and Alzheimer's disease. Elevated homocysteine levels can occur because of many factors, including genetic factors such as the presence of a genetic polymorphism of the enzyme that converts folic acid to its physiologically active form 5-methylolate. Elevated homocysteine levels are correlated with low intake of some cofactors or the genetically determined inability to activate the cofactors. In these cases, supplementation with 5-methylfolate, pyridoxal-5-phosphate, methylcobalamin, and betaine can be corrective (18, 19). Hispanics have displayed a relatively elevated occurrence of this functional polymorphism (i.e., MTHFR C677-T, aka rs1801133) on the gene encoding the enzyme methylene-tetrahydrofolate reductase (MTHFR) (20–22). MTHFR catalyzes the conversion of the folic acid metabolite (5, 10-MTHF) to its physiologically active form (5-MTHF), a co-substrate for homocysteine (Hcy) re-methylation to methionine (23). The higher prevalence of this polymorphism in Hispanics compared to what is seen in other populations translates to a lower degree of activation of the folic acid. Therefore, this enzymatic limitation can be overcome by supplementation with the active form, 5-MTHF.

Pyridoxal-5-phosphate, methylcobalamin, and betaine (trimethylglycine) also play an indirect role in homocysteine metabolism (4). This polymorphism presents alterations (errors) in DNA nucleotides a C→T missense mutation (cytosine to thymidine) at site 677 of the MTHFR cDNA, leading to a valine exchange at amino acid 222, encoding a thermolabile enzyme with decreased activity that results in raised levels of the metabolic by-product Hcy (i.e., hyperhomocysteinemia) (24, 25).

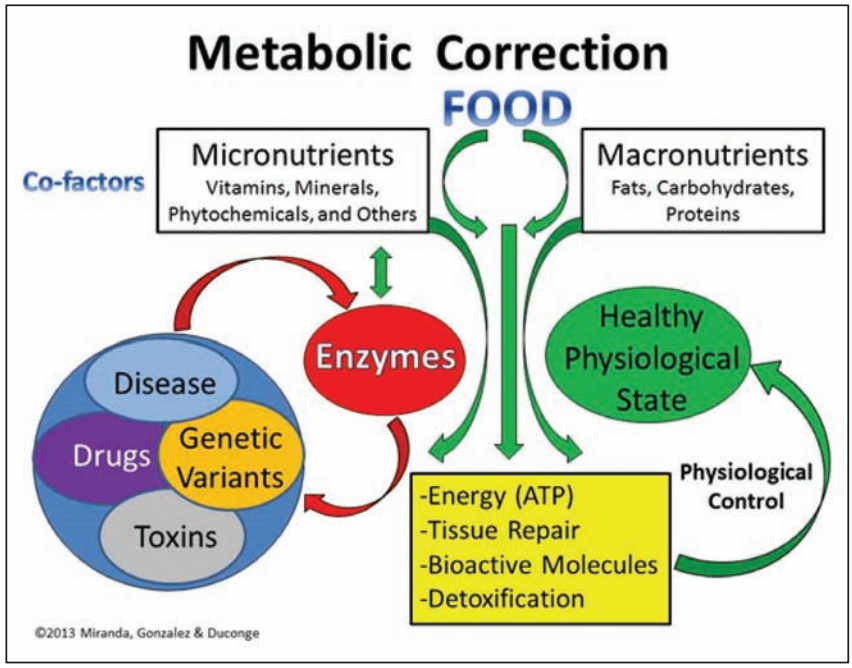

Figure 1 illustrates the concept of *Metabolic Correction*. Food provides macro- and micronutrients that are required for energy production; in addition, they provide precursors of functional and structural molecules necessary for a healthy metabolism, tissue repair, and detoxification. Genetic variants, illnesses, pollutants, and drugs can increase the demand for certain nutrients. If the demand goes beyond tissue storage capacity, then a co-factor insufficiency arises. Co-factor insufficiencies will reduce specific enzymatic activity. Reductions in enzymatic activity can influence energy creation, tissue repair, and the synthesis of bioactive molecules, detoxification, all of which will alter the homeostasis of the healthy physiological state. Red arrows means malfunction due to nutrient insufficiency. Green arrow means proper function due to sufficient nutrient and enzymatic activity.

The concept of Metabolic correction

Metabolic correction provides a biochemical description of the utilization of nutrients as enzymatic cofactors, precursor molecules, regulator molecules, and metabolites for preventive and therapeutic action against disease (11). This functional biochemical-physiological concept clarifies how improvements in cellular biochemistry and adaptive physiologic control help the body achieve metabolic or physiological optimization. Figure 1 illustrates this concept.

History of Metabolic correction

The idea of metabolic correction is based on the work of several iconoclastic medical pioneers (26). In 1947, Dr. Roger J. Williams contributed to the development of the understanding of the biochemical–genetic origin of disease with the development of the concept of "biochemical individuality" (27). He described anatomical and physiological variants among individuals and how they related to their distinctive responses to the environment and their particular physiologies. He coined the term "biochemical individuality" and described how it relates to the uniqueness of the nutritional requirements for optimal functioning among different individuals. Early examples of

molecular biology and molecular medicine were originated by Dr. Linus C. Pauling, in a landmark article on the mechanism of sickle cell anemia (28). Dr. Pauling generated a new vision of the origin of disease, grounded upon the acknowledgment that specific mutations of the genes can create an altered biochemical environment and, thereby, the modified physiological state associated with a particular disease. In 1950, Dr. Roger J. Williams invented the term "genetotrophic disease" to describe diseases which result when genetically determined nutritional needs are not met by an individual's diet, resulting in poor gene expression (29) and the loss of adaptive physiologic control. Patients with genetotrophic conditions have an increased need for 1 or more nutrients if they are to achieve healthy physiologic functioning. Adaptation to nutrient deficits might cause no apparent short-term effects but may eventually result in chronic disease. These genetotrophic conditions can be clinically associated with functional polymorphisms on genes encoding key components of the altered metabolic pathways. As the homocysteine example demonstrates, biochemical control can be restored when sufficient of the required nutrients (cofactors) are provided to correct the deficit. Genetotrophic conditions improve greatly with the addition of appropriate amounts of the required nutrient. Examples of genetotrophic conditions include muscular dystrophy, allergies, psychiatric diseases, cardiovascular conditions, arthritis, multiple sclerosis, and cancer (25). Many chronic conditions can be regarded as polymorphism-associated genetotrophic conditions if a given nutrient(s) fills a specific metabolic need it should be added to the diet of a patient suffering from that condition, and should result in an improvement to the patient's. Dr. Williams's research approach was an early forerunner of personalized or functional medicine, which is a current focus of medical research and practice. Diet and nutritional status influence phenotypic function and control gene expression through epigenetic-related mechanisms. Dr. Williams pointed out that human biochemical variation in function was of relevance to understanding health and disease mechanisms, and this idea is a primary consideration in today's research environment of personal genomics and individual targeted medical solutions (30).

Between the 1950s and 1960s, Dr. Henry Turkel was the first to demonstrate clinically that nutrition and supplementation can modify gene expression and biochemical controls in Down's syndrome (31). Turkel was probably also the first clinician to use metabolic correction as therapy when he influenced harmful gene expressions in children with Down's syndrome by removing harmful accumulated metabolic by-products from a given patient's system with nutrition and high-dose supplements. He was able to bring about an improvement in cognition, physical health, and physical appearance in Down's syndrome patients (31).

In 1973, Dr. Bernard Rimland used an enhanced B-complex formula with extra vitamins B5 and B6 plus vitamin C and iron to aid emotionally disturbed children. Out of 190 severely disturbed kids, 164 showed some improvement over 90 days (32).

In 1980, Dr. Ruth Flinn Harrell and her colleagues gave a comprehensive vitamin and mineral supplement to a group of mentally retarded children. It took only 4 months of supplementation to increase the children IQs by 5.0 to 9.6 points. The unsupplemented children acting as controls showed no significant changes. Considering that these patients had different retardation syndromes (including Down's syndrome), the IQ gains were highly significant (33).

The word "orthomolecular" was introduced by Dr. Linus Pauling in a paper in the journal Science in 1968 (34). The idea proposed by orthomolecular medicine was that the provision of the proper molecule could correct a metabolic imbalance and restore the biochemical control system. Dr. Pauling defined orthomolecular psychiatry as the treatment of mental conditions with the use of the optimum molecular environment for the mind, which could be brought about by regulating the concentrations of substances normally in the body. He later broadened this definition to include the health of the whole individual, describing the totality as orthomolecular medicine (11). Genetic factors influence not only the phenotypes of individuals but also their biochemical environments. The metabolism and its myriad chemical pathways have substantial genetic variability, and illnesses such as atherosclerosis, cancer, schizophrenia, and depression are associated with unique biochemical abnormalities (high homocysteine, reduced oxidative phosphorylation, increased kryptopyrrole, decreased serotonin) which may be causal or contributing factors of the given illness. Importantly, the hypothesis that "optimum" molecular concentrations of substances may be achieved solely by dietary means has little direct supporting data. The need for essential nutrients (vitamins, essential amino acids, and fatty acids) is expected to differ for each person (individual) from the (average) daily amounts recommended for the general population (1, 10).

The concept of functional medicine was created by Dr. Jeffrey Bland in 1991. Functional medicine is a form of individualized medicine that deals with disease prevention and the underlying causes of illness instead of treating just the symptoms. It works by identifying the "core clinical imbalances" that underlie different conditions. Imbalances arise from environmental conditions, such as diet, nutrients (including air and water), toxins, exercise, and trauma, together with the individual's genetic predispositions, attitudes, levels of psychological stress, and beliefs. The "core clinical imbalances" arise from malfunctions in biochemical and physiological controls. The multifold range of involved include hormone and neurotransmitter, oxidation-reduction, mitochondriopathy, detoxification, biotransformation, immune response, inflammation, and digestive, microbiological, and structural imbalances from

cellular membrane function to the organ systems. Improving the control of an individual's biosystem, that is, improving his or her physiological balance, is the precursor to restoring health and involves more than treating symptoms (11). Functional medicine deals with the management of chronic disease by integrating the interventions at multiple levels to restore the functionality and health of patients. Functional medicine is grounded in basic science and systems theory, combining research from various disciplines into clinically relevant models of disease pathogenesis and clinical management. Dr. Bland's 1999 book "Genetic Nutritioneering" explains how proper nutrition and supplementation can modify genetic expression and incorporates the latest findings in epigenetics to create the best possible health outcomes (35).

More recently, Dr. Bruce N. Ames presented his Triage Theory of optimal nutrition (3), mentioned briefly above. When the human body is deprived of a nutrient to such a degree that this nutrient can be said to be depleted, the human body prioritizes how the remaining vitamins and minerals are to be used. In clinical medicine, triage means deciding which patients to treat when faced with limited resources. When faced with a nutritional deficit, the human body decides which biological functions to preserve in order to maintain the vital functions of the system, giving the individual the best chance to survive and reproduce. Per the evolutionary imperative, the body will always direct nutrients toward short-term survival; the evolutionary concern is survival to reproduce. Chronic disease, aging, and ultimate longevity are largely irrelevant for evolutionary success. Thus systems for the regulation and repair of cellular DNA and proteins that optimize health, prevent chronic illness, and increase lifespan are actively depleted. Dr. Ames's research explains how, in the presence of nutritional deprivation, the system controls may promote age-related diseases for short-term gain and stability. Therefore, the adequate intake of micronutrients decreases the risk of those degenerative diseases and conditions associated with aging, such as cancer, cognitive decline, and immune dysfunction (10, 36–39). While short-term deficiencies or insufficiencies are common, mainstream physicians may overlook them, as their primary clinical focus is the treatment of a specific disease's symptomatology.

Dr. Michael J. Gonzalez and Dr. Jorge R. Miranda-Massari introduced the term metabolic correction in 2011 (40) to describe a mechanism by which nutrients can correct biochemical disruptions that promote a diversity of dysfunctional or degenerative states. Metabolic correction includes the previously described system concepts to explain how improvements in the control of cellular biochemistry may help the body achieve and maintain health. Metabolic correction acts on the impaired biochemical reactions that are associated with a variety of disease states. Metabolic correction is the fine tuning of the cellular biochemistry with the goal of improving function.

Conclusion

Nutrient deficiency or insufficiency-related diseases are the end products of a series of cellular biochemical adaptations that are caused by the lack of enzymatic cofactors. The biochemical systems experiencing those lacks will compensate for them, in the short term, but the adaptation is incomplete. Deficiencies of these micronutrients may not be severe enough to produce fast and clear clinical symptoms, but the long-term consequences could lead to a greater risk of a major disease. The lack of cofactors may affect the body's ability to maintain good health and its capacity to resist and reverse disease. Nutrient insufficiencies and imbalances also affect the body's ability to recover from exercise and surgery and affect, as well, the capability of the brain to function at a high level.

Resumen

Las funciones del cuerpo humano dependen de una plétora de procesos bioquímicos, muchos de los cuales son interdependientes. La velocidad y el grado de completamiento de muchas reacciones dependen de la disponibilidad de precursores y de las enzimas correspondientes. La actividad enzimática depende de la disponibilidad de cofactores micronutrientes tales como vitaminas y minerales. Para poder alcanzar un estado fisiológico saludable, el organismo requiere que las reacciones bioquímicas ocurran a una velocidad controlada el cual podríamos denominar como un equilibrio metabólico óptimo. La demanda de nutrientes necesarios para alcanzar el equilibrio metabólico óptimo puede afectarse por la composición genética, los patrones alimenticios, traumas, enfermedades, toxinas, medicamentos y los estresores ambientales. En la parte 1 se presenta el concepto de corrección metabólica y como el mismo está cobrando una creciente importancia según aumenta nuestro conocimiento de las variantes genéticas que controlan las reacciones enzimáticas responsables de los disturbios metabólicos que permiten o promueven el estado patológico. Además en esta primera parte se resume las contribuciones de científicos prominentes a nuestro entendimiento de la importancia de los micronutrientes en la salud y enfermedad así como el desarrollo del concepto de corrección metabólica.

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Metabolic Correction: A Functional Biochemical Mechanism against Disease • Part 2: Mechanisms and Benefits

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A healthy physiology depends on a plethora of complex interdependent biochemical reactions. In order for these reactions to occur suitably, the enzymes and cofactors that regulate their flow must be present in the proper balance. The term metabolic correction is used to describe a biochemical–physiological process that improves cellular biochemistry as a means to an individual's achieving metabolic or physiological optimization. Part 2 discusses how metabolic correction, through the increase of cofactors, can supply unmet enzyme needs and compensate for nutritional deficiencies induced by improper nutritional intake or by the increased demand for nutrients caused by genetics, health conditions, medications, or physical or environmental stressors. Nutrient insufficiencies are causing an increase in morbidity and mortality, at great cost to our society. In summary, metabolic correction improves enzymatic function and satisfies the increasing demand for nutrients. Metabolic correction can have a significant impact on the reduction of morbidity and mortality and their financial cost to our society and contribute to improving health and well-being. [*P R Health Sci J 2015;34:9-13*]

Key words: Metabolic correction, Chronic disease, Genetotrophic disease, Biochemical individuality, Nutrient insufficiency, functional medicine, Orthomolecular medicine

Metabolic correction is the use of specific synergistic micronutrient combinations that serve as precursors and cofactors in their most biologically active forms to facilitate the reactions that can form all the molecules needed to build and support the structures and functions that maintain and improve health and quality of life. Multiple variables can influence the amount, form, and combination of micronutrients needed for optimal functioning, taking into account genetic diversity; the wide variations in nutritional habits; the environmental toxins present in food, air, water (and other beverages); disease states; trauma; the use of medication or recreational drugs; and other aspects of lifestyle, such as the amount of sleep an individual gets.

Why Metabolic correction?

1. Unmet nutritional needs

A person with poor nutritional habits may have nutritional needs that are not satisfied. However, this situation can also occur due to the inferior nutritional value of available food, lack of availability of nutrient-dense foods, and nutrient loss that occurs with the cooking process (1). Consuming a wide range of well-chosen foods may help an individual obtain the required nutrients to attain a healthy state. Today's foods are not as nutritious as those eaten in the past, which may lead to low-level deficiencies. The nutritional values of the fruits and vegetables that people eat are not always the same as what can be found on a given food composition table. One study (2) that compared nutritional values as set forth by 1950 USDA food composition tables with those values detailed in more recent tables (1999) determined that such values had depreciated significantly, with declines in the levels of protein (6%), calcium (16%), phosphorus (9%), iron (15%), riboflavin (38%), and vitamin C (20%), among others, being reported (2). There is an environmental dilution effect by

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which yield-enhancing methods such as fertilization and irrigation may decrease nutrient concentrations. Recently, data have emerged suggesting that genetically induced increases in yield may also have a nutrient-dilution effect. Modern crops that grow larger and faster are not necessarily able to acquire and store nutrients at the corresponding rate. US and UK government statistics show that there has been a decline of up to 76% in trace minerals in fruits and vegetables over a 51-year period (1940 to 1991) (3). It should be noted, however, that consuming organic foods can at least partially offset this loss, with the added benefit of reducing the amounts of pesticide, herbicide, chemical fertilizer, antibiotics, and hormones that a given person might ingest. Organic fruits and vegetables are nutrient-dense and have lower toxic loads. There is a need for people to increase their consumption of fruits and vegetables in order to get the same nutritional intake that individuals in the past did. Americans and people from first-world countries typically eat more than the recommended upper limits of added sugars, refined carbohydrates, and added fats and oils (10). Such diets provide fewer nutrients than the minimum needed for long-term health.

2. Adverse side effects of medication and iatrogenic deaths

In the US more than 100,000 deaths due to adverse drug reactions (ADR's) to medication (4) are reported annually. Additionally, the Institute of Medicine (IOM) has reported that medical errors could be responsible for from 44,000 to 98,000 deaths, annually, in the US (5). The incidence of serious and fatal ADRs in US hospitals is higher than is generally recognized. Fatal ADRs are, approximately, the fourth leading cause of death in the US (4). The World Health Organization recognizes that ADRs rank among the top 10 leading causes of mortality (6). In addition to death and suffering, the cost of medication-related mortality and morbidity (MM) in the US is exceedingly high and continues to increase. A pharmacoeconomic study published in 1995 estimated this cost (among ambulatory patients in the US) to be $76 billion per year (7). A follow-up study concluded that the cost increased to $177 billion per year in 2000 (8). At this rate of increase, the cost of medication related to MM was estimated to be $700 billion by 2013. A recent study from Germany serves as further evidence of the high costs of adverse drug events. Total health care costs related to ADEs from outpatient treatment were estimated to be 816 million Euros (9).

Adverse effects from medications have many different causes. These have been classified by the type of reaction and named with a letter and refer to the relationship of the reaction with the dose amount or buildup, time, genetic particularities, and interactions with other drugs or environmental/nutritional elements (10). Probably the most common ADR is an extension of the pharmacologic effect beyond the desired, intended effect, in which case this effect would probably be a toxic one. However, other causes of ADRs include immunologic reactions (including allergies) and interferences with metabolic, developmental, or reproductive processes (such as teratogenesis, carcinogenesis, pharmacokinetic interactions, and drug-induced nutrient depletion). One group that is particularly susceptible to ADRs is older adults. The main reason for this is that they metabolize (neutralize) and eliminate a given drug more slowly than younger individuals do, which makes these older people more susceptible to overdose. They also tend have more health problems and, therefore, consume more medication, and, finally, they are more prone to drug-induced nutrient depletion. This can occur because a drug can interfere with the absorption, distribution, metabolism, or elimination of micronutrients (11). Since medication-induced nutrient depletion is not often recognized as a cause of adverse effects, it is only infrequently treated as such.

Drug-induced nutrient depletion is usually a slow process that can lead over time to a diversity of induced health problems and increased health costs (12). Patients with chronic diseases are at increased risk of drug–nutrient interactions due to those patients' long-term use of multiple medications. If drug therapy is required, providing metabolic correction can compensate for such interactions as well as reduce adverse side effects and improve therapeutic outcomes (13–18). Medications such as diuretics, anticholesterol agents (statins), and antidiabetics, all of which produce nutrient depletion, may induce new medical conditions or complicate current conditions (14).

3. Compensation for the augmented demand for nutrients secondary to toxins and disease

The sustained exposure to substances such as drugs, alcohol, tobacco, environmental contaminants, and metabolic by-products can cause cumulative damage over time and can be an important contributor to chronic disease. Detoxification of these harmful substances requires enzymes that are activated by various nutrients (vitamins, minerals, amino acids, and other cofactors) which are needed in sufficient amounts to work effectively. Exposure to alcohol, tobacco, and environmental toxins creates an increased metabolic demand for nutrients for detoxification (19). In order to prevent toxicity and chronic disease, it is important to ensure that a given individual is consuming sufficient amounts of the required nutrient cofactors (20, 21).

Disease states and injuries may produce additional nutritional demands for tissue repair, energy production, and other metabolic processes necessary for health. An example of increased nutritional demand would be a patient with significant burns may lose substantial protein and essential nutrients that need to be replaced so that healing may occur (22). Surgery elevates the requirements for zinc, vitamin C, and other nutrients involved in tissue healing at the cellular level (23). Fractured bones need calcium, magnesium, and vitamins C and D in order to heal (and do so properly) (24). Infections activate the immune

system and increase the demand for zinc, B-complex vitamins, and vitamin C (25). Mitochondrial dysfunction has been linked to low levels of cellular energy, problems with muscle relaxation, and pain. Chronic fatigue and fibromyalgia are two potential results of mitochondrial dysfunction Nutritional mitochondrial support may be an important treatment modality for restoring adequate energy production that promotes normal physiologic functions including muscle relaxation, improved nerve function and pain relief.

Metabolic correction mechanism: Molecular concentrations and rate of reaction (Km concept)

Most chemical reactions occurring in biological organisms are catalyzed by enzymes. These reactions involve the formation by the enzyme and a substrate of a complex and the subsequent breakdown of this complex to form the product of the reaction. Usually the breakdown of the complex is the rate-determining step.

Michaelis-Menten kinetics describes enzyme kinetics and relates the reaction rate to the concentration of a substrate. The Michaelis constant, Km, is the substrate concentration at which the reaction rate is at half-maximum and is an inverse measure of the substrate's affinity for the enzyme. A small Km means a high affinity, which will produce a faster rate of reaction (26). Some mutations raise the Km and lower the coenzyme binding affinity. This Km concept applies especially to cofactors that function as true substrates of the enzyme in question. Other cofactors that increase enzyme activity are better described by equations other than Km.

The speed of an enzyme-catalyzed reaction is approximately proportional to the concentration of the reactant, until concentrations that saturate the enzyme are obtained. The amount of cofactor needed to achieve saturation is larger for an inefficient enzyme than for a normal enzyme. For such a defective enzyme, the speed of the reaction rate can be increased with a higher substrate concentration. The law of mass action explains that as the vitamin and mineral concentrations increase, enzyme efficiency increases. Defective enzymes may result in a lack of biochemical control with the accumulation of metabolic by-products. These considerations obviously suggest a rationale for metabolic correction, in which the required cofactors are provided in the amounts needed to improve enzymatic function. This increased enzyme efficiency may allow greater system adaptation and the accommodation of a genetic defect. The process is one of negative feedback and follows the chemical principle of Le Chatelier. This principle states that when stress is applied to a system in equilibrium, the system will readjust itself to minimize that stress. In this case, there is an unfavorable equilibrium of the active enzyme that can be compensated, with the addition of the necessary nutrients, this will allow adaption to a more physiologically favorable metabolic state (27).

To some extent, human genetic diseases caused by defective enzymes can be ameliorated by the use of high doses of the vitamin component of the corresponding coenzyme so as to at least partially reestablish the enzymatic activity (26). Various single nucleotide polymorphisms in which the variant amino acid reduces coenzyme binding demonstrate that enzymatic activity can be improved by increasing cellular concentrations of the cofactor through high-dose nutrient therapy (28, 29). It appears that 33% or more of the mutations in a disease gene respond to high concentrations of nutrient cofactors (26). These mutations are projected to result in diminished enzyme binding affinity for corresponding coenzymes, of which vitamins and minerals are included. There are many hidden genetic defects (inborn or acquired), and it is probable that many individuals have higher genetic requirements for several micronutrients (26, 30).

The insufficient consumption of vitamins and minerals in one's diet may lead to DNA damage, mitochondrial decay, and other pathologies (1). Ames's evolutionary allocation of scarce micronutrients by enzyme triage explains why DNA damage is commonly found when there is micronutrient deficiency (1). In addition, Motulsky and others had argued that many of the common degenerative diseases, including cardiovascular disease and cancer, are the result of the imbalance between nutritional intake and genetically determined needs (31-34). Folic acid and vitamin B12 work towards maintaining nuclear and mitochondrial genome integrity. Studies with human cells show that shortages of these vitamins cause an array of complications in the nuclear and mitochondrial DNA, which complications can be diminished with increased folate and B12 concentrations. In order to obtain the protective effect of these vitamins, they are needed in concentrations exceeding existing recommended dietary intakes (folate>400 μg/day, and vitamin B12>2μg/day) (35).

Physiological malfunction due to the insufficiency of vitamins and minerals can lead to organ and tissue function problems, which can include poor drug metabolism, insufficient neurotransmitter production, and impaired immune defenses (36). Chronic subclinical under nutrition may reduce immune capability and central nervous system proficiency while increasing the complications related to pre-existing degenerative diseases. This approach to avoiding insufficiencies and promoting health by improving enzyme efficiency and thereby metabolism and physiology is the basis of metabolic correction (37).

The use of high-dose B vitamins to counteract a poor Km is an example of metabolic correction. It has been estimated that one third of the mutations in a given gene cause, in the corresponding enzyme, decreased binding affinity (increased Km) for a coenzyme, thereby decreasing the reaction rate (27, 38). Therefore correction can be achieved by increasing the amount of the cofactors; this would compensate for the decrease

affinity and therefore maintaining an adequate reaction rate. Approximately 50 different human genetic illnesses that are caused by the inferior binding affinity of the mutant enzyme for its coenzyme can be mitigated by providing high-dose B vitamins, which vitamins increase the levels of the corresponding coenzyme; numerous polymorphisms also result in an enzyme's lowered affinity for its vitamin coenzyme (27, 38) and thus may, in part, be improved. Vitamins also have certain influences on metabolism which are not related to coenzyme effects. Vitamins, minerals, and other cofactors can have actions that affect the biochemistry of the cell and thus the function of specific cellular organelles (such as the mitochondria), on hormone levels, or supra-molecular structures within a cell (26).

Metabolic correction results in two important biological outcomes. The first is the optimization of cellular function (which occurs as enzymatic efficiency improves). The second is the adaptive biological effect that corrects abnormal cell function and reverses the biochemical disarray of the disease process. The optimal consumption of micronutrients and metabolites differs with age, environmental factors, and genetics. Metabolic correction should tune up an individual's metabolism and increase his or her health in a safe, cost effective way, which is particularly important for the poor and the elderly (38).

Stages of nutrient insufficiency

A nutrient deficiency is defined as a physiological state in which the depletion of a nutrient is linked to the damage of certain biochemical reactions and a lack of well-being. Marginal deficiency or insufficiency is the initial stage of the deficiency and represents the initial shortage of the nutrient needed to supply the required biochemical pathways in order to optimize physiology and, thus, be able to reach a healthy state.

In order to discuss nutrient depletion in the body, it is helpful to classify the process as occurring in 5 stages: Storage depletion, biochemical depletion, physiological depletion, clinical depletion, and anatomical damage. In the storage depletion or preliminary deficiency stage, the body's reserves of cofactors gradually decline. The biochemical stage, or secondary deficiency stage, is when the functional enzymes are decreased and the body's systems experience a reduction in physiological function due to the lack of necessary cofactors. In the physiological or tertiary deficiency stage, enzyme activity is sufficiently impaired as to affect immune and behavioral parameters. Personality changes can occur and there is an increased susceptibility to disease. There may be a variety of non-specific symptoms arising, such as loss of appetite, depression, irritability, anxiety, insomnia, or somnolence; the person may not be sick enough to seek medical attention, but his or her general health would be poor. The clinical deficiency stage is when overt illness occurs. It is important to note that the nutritional foundation of a chronic illness may not be identifiable because of limited knowledge and recognition of this concept. Finally, the anatomical or final deficiency stage is when clinical stage has not been corrected for a considerable period of time and the death of the individual will occur if immediate nutritional intervention is not initiated. The suboptimal ingestion of vitamins just scarcely above levels causing vitamin deficiency is a risk factor for chronic diseases and is common in the general population, especially in the elderly (39–41).

Metabolic correction is accomplished through the supplementation of micronutrients (such as B-complex vitamins, CoQ10, lipoic acid, etc.) that have been demonstrated to be extremely safe. Half of the American population is estimated to be taking vitamins on a daily basis. There has not been a single death from any vitamin in years. Gross overdoses of iron (not a vitamin) amount to only 2 deaths per year, and 59 deaths were attributed to aspirin in 2003 (42).

Conclusion

Nutrient deficiency or insufficiency diseases are the end products of a series of nutrient-related reactions. Biochemical systems compensate for these deficiencies in the short term, but the adaptation is incomplete. Micronutrient deficiencies may not be severe enough to produce immediate and clear clinical symptoms, but the long-range implications of such deficiencies are that they lead to increased risk of disease. Small decreases in enzyme cofactors may present without specific symptoms or with some vague non-specific indications, such as lethargy, irritability, insomnia, or difficulty in concentration. A lack of cofactors may affect the body's ability to maintain good health, to resist and disease, and to recover from exercise, surgery, and disease; such a lack may also affect the ability of the brain to function at a high level. Detecting and treating illness at its earliest stages of cellular biochemical abnormality rather than waiting for the appearance of clear clinical symptoms reduces overall costs and patient complications. We propose to expand the concept of therapeutic nutrition to include the treatment of chronic diseases by metabolic correction.

Resumen

La fisiología saludable depende de una plétora de reacciones bioquímicas interdependientes y complejas. Para que se produzcan adecuadamente estas reacciones, las enzimas y cofactores que regulan su flujo deben estar presentes en un equilibrio adecuado. El término corrección metabólica describe el proceso bioquímico-fisiológico que mejora la bioquímica celular para lograr la optimización fisiológica. Esta parte 2 discute cómo la corrección metabólica mediante el aumento de cofactores puede suplir necesidades enzimáticas insatisfechas, compensar deficiencias nutricionales inducidas por ingesta inapropiada, por necesidades aumentadas por genética, condiciones de salud, medicamentos, y por estresores físicos

y ambientales. Las insuficiencias de nutrientes están causando un aumento en la morbilidad y la mortalidad a un gran costo a nuestra sociedad. En resumen, la corrección metabólica mejora la función enzimática satisfaciendo la demanda de aumento de nutrientes. La corrección metabólica puede tener un impacto significativo en la disminución de la morbilidad y mortalidad y su costo financiero a nuestra sociedad y contribuir a mejorar de la salud y el bienestar.

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