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*]

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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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