

• SPECIAL ARTICLES ON HEALTH SCIENCES RESEARCH IN PUERTO RICO •

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 conducive 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).

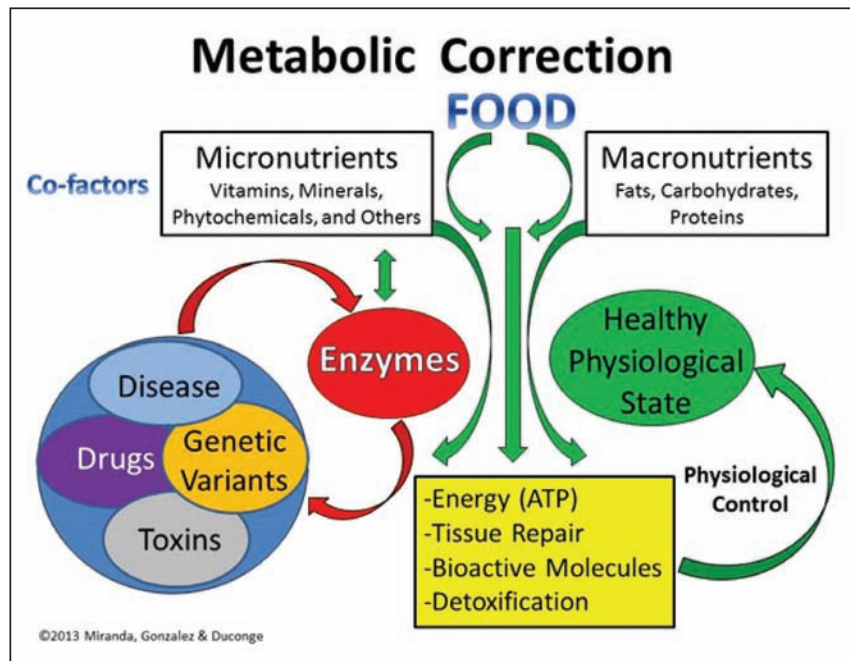


Figure 1 illustrates the concept of *Metabolic Correction*. Food provides macro- and micronutrients that are required for energy production; in addition, they provide precursors of functional and structural molecules necessary for a healthy metabolism, tissue repair, and detoxification. Genetic variants, 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 la 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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