Chapter 23

Buteyko Breathing Technique and Ketogenic Diet as Potential Hormetins in Nonpharmacological Metabolic Approaches to Health and Longevity

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23.1 HEALTH PARADOX AND PARADIGM

The majority of modern research into health and longevity is carried out to create medical drugs targeted toward specific factors and symptoms characteristic of the particular diseases and conditions. However, the last 50 years have shown a paradoxical development in the national health systems. According to the American Hospital Association data [1], the total national health expenditure in the United States increased approximately 7.5 times from 1970 to the present, and the expenditure on prescription drugs increased 10-fold [2].

Health expenditure as a percentage of GDP almost tripled, from 7% to 18% [3]. However, at the same time, the extent of lifestyle diseases has increased many-fold in a single lifetime. The obesity rate has doubled since the 1970s for adults and tripled for children [4]. The rate of diabetes has increased over 10 times [5]. The extent of cancer doubled, and according the prognosis by the WHO, cancer cases are expected to surge by 70% worldwide in the next 20 years in an imminent "human disaster." This means that at least half of us will suffer cancer during our lifetimes [6]. Chronic lifestyle disease expenditures account for 86% of total national health expenditures [7]. The same trends exist worldwide as in the United States.

Thus the paradox: the more money we spend on a problem—the bigger the problem becomes. To break this paradoxical development and to handle the increasing load on public health we need a paradigm change. Could hormesis be a part of the solution and this paradigm change? This chapter aims to introduce and discuss the use of nonpharmacological approaches, synergetic effects of their combined use, and the associated hormetic effects.

23.1.1 Noncommunicable Diseases, Metabolic Syndrome, and Aging

Noncommunicable diseases (NCDs) are the single biggest factor dominating health and longevity of modern humans. The WHO states that 70% of global disease load is caused by NCD, which are also responsible for about 70% of all deaths globally [8]. The most common causes of NCD are strongly correlated to metabolic and behavioral risk factors, and contribute to four key metabolic changes that increase the risk of NCDs:

(1) Raised blood pressure
(2) Overweight/obesity
(3) Hyperglycemia
(4) Hyperlipidemia

To better understand the risk of NCDs, let us consider the positive and negative feedback loops (NFbLs) in human health.

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Positive feedback loops amplify the changes which tend to move a system away from its equilibrium, making it more unstable. NFbLs dampen the changes which tend to move a system closer to equilibrium, making it more stable. The four metabolic risk factors play a big causal role in NCDs and are a major contributor to MetS. MetS is a typical example of a positive feedback loop that brings the body away from the stable state promoting the continuous emergence of new symptoms. Using pharmacological drugs to handle each symptom exacerbates the situation, promoting new symptoms. The positive feedback loop upregulates the body's metabolism at each visit to the doctor and new medication is prescribed, which creates new cascade of iatrogenic side effects and symptoms. Iatrogenesis is one of the primary causes why the NCDs including asthma, arthritis, COPD, neurodegenerative diseases, and diabetes are still considered incurable by conventional health care [9].

Constantly feeding the positive feedback loop promotes the second law of thermodynamics—entropy, chaos, and disorder [10]. Albert Szent Gyorgyi has described cancer as "an increased state of entropy, where randomness and disorder predominate" [11]. For the vast majority of cancers, risk factors are environmental or lifestyle related, thus cancers are mostly preventable NCDs [12]. The combination of several risk factors leads to rise of inflammatory reactions, building up the state of chronic inflammation that slowly becomes rooted in the body [13]. That is how the process of aging starts, which is based on the second law of thermodynamics, where entropy and disorder predominate and where the belief that it only applies to closed systems has been overturned [14,15].

23.1.2 Pharmacological vs. Nonpharmacological Approaches

Lifestyle diseases are multifactorial in their very essence. Pharmacological targeted approaches often combine chemical substances that target different factors of the disease, leading to adverse side effects of drug interaction that can be detrimental to health in their own right, leading to iatrogenic comorbidities [16]. Iatrogenic effects are a major issue in modern health care. According to Macary and Daniel, death from medical care itself is the third leading cause of death in the United States [9]. There is an explicit and urgent need to create and implement approaches that target the causes of lifestyle diseases instead of the symptoms.

A counterpart of pharmacological and invasive approaches are metabolic approaches that are multifactorial in their essence. These approaches, addressing metabolic risk factors lying at the core of the illness are normalizing its causes instead of targeting single symptoms. These approaches are most often both nonpharmacological and noninvasive. These nonpharmacological metabolic approaches (NPMA) shift the emphasis from full dependence on medical drugs and invasive treatments toward healing through prevailing drug-free optimization of metabolism [17,18].

23.1.3 Paradigm Shift—From Patient Role to Personal Responsibility

NPMA require full involvement of the individual in the process of healing, as it is carried out exclusively through training and lifestyle interventions. The notion of a health-compromised person taking full responsibility for their own health is both an inner driver requirement and a prerequisite of success for all NPMA. The individual's role changes slowly from being client/patient to being an active participant in charge of the daily execution of the process being deeply involved in the self-healing work through combination of lifestyle change and training.

This bigger role of training implies a much greater role for hormesis in the metabolic therapeutic strategies in the future, as many hormetins are by definition effects of low-dose stress induced by training and change in different patterns of lifestyle. The powerful hormetic effects on the process of healing and recovery can be effectuated through the process of structured training. This "window of opportunity" for the NPMA is created by prioritizing to start with the changes that are most crucial and promote maximum effectiveness and thus help to establish strong and lasting process of healing. This can be done through prioritizing enhancement of the energy supply and utilization, by coordinated effort on the fields of optimization of breathing, nutrition, physical training, and lifestyle intervention.

23.2 THE ROLE OF BREATHING AND NUTRITION IN NONPHARMACOLOGICAL METABOLIC APPROACHES FOR HEALTH AND LONGEVITY

As mentioned before, the four metabolic risk factors play a big causal role in NCDs and constitute a major contributor to MetS. Therefore, it can be hypothesized that by kick-starting the process of enhancement of the energy supply and utilization primarily through optimization of breathing and nutrition we can create an intensive stimulus for the process of healing.

The notion of optimal breathing and nutrition at the cellular level is both a matter of common sense and scientific evidence. These processes constitute the two main paths of energy supply and utilization from the environment into the human body. Despite this fact, both optimization of breathing and optimization of nutrition are the two mostly undervalued and widely ignored areas in the conventional health care and medical practice.

Looking at the human body's energy supply chain on the level of common sense, we consider breathing and nutrition as the two main sources of energy that have a direct impact on our daily well-being. Looking at the cellular level, the situation is the same. Human cells use respiration to oxidize common nutrients (sugar, amino acids, and fatty acids) with the most common oxidizing agent (oxygen) to form chemical energy ATP.

Buteyko breathing technique (BBT) [19] and ketogenic diet (KD) are two methods of optimization of breathing and nutrition that show a powerful synergetic effect when used in combination. Both methods can be used in context of drug-free metabolic therapy for a range of lifestyle diseases as well as possible strategy for longevity and are simple and inexpensive lifestyle changes that lead to better health and promote longevity.

BBT is a method of optimization of automatic breathing patterns that promotes better cellular oxygenation [19]. KD is a way of eating (WOE) that promotes more effective use of energy by shifting cell metabolism toward using fats instead of carbohydrates as a primary energy source.

There are studies that suggest that some of the positive effects of BBT and KD are due to activation of the low-dose hormetic stress pathways.

23.3 BUTEYKO METHOD AS STRATEGIC NONPHARMACOLOGICAL METABOLIC APPROACHES FOR BREATHING OPTIMIZATION AND ITS POTENTIAL HORMETIC EFFECTS FOR HEALTH AND LONGEVITY

BBT is an education program aimed at reversing the chronic hyperventilation syndrome (CHVS), which is a quite common but inadequately researched breathing pattern disorder (BPD), and often overlooked as a cause of many symptoms. Dr. Konstantin Buteyko developed BBT in 1952 to treat hypertension. Fifty years of practice demonstrated this method as being effective for dealing with a range of NCDs secondary to CHVS.

It is estimated that 10% of people consulting their doctor suffer from CHVS [20,21]. Doctors rarely diagnose the disorder or even look for CHVS as a diagnostic possibility [22,23]. According to Folgering [24], "hyperventilation is defined as breathing in excess of the metabolic needs of the body, eliminating more carbon dioxide than is produced, and, consequently, resulting in respiratory alkalosis and an elevated blood pH." The main goal and vision of BBT is long-term normalization and optimization of automatic breathing patterns through gradual physiological habituation to breathing less, eventually stopping hyperventilation and normalizing alveolar CO_2 levels. In this way, the same processes which initially triggered hyperventilation to become chronic are reversed. In general, there are several approaches to breathing exercises:

- Hypoxic exercises
- Hypercapnic (hypercarbic) exercises
- Breathing techniques based on the reduction of the rate of breathing
- Breathing techniques for reduction of minute ventilation/breathing volume

BBT combines the best of all of these techniques. In its country of origin (Russia) it is also named more descriptively as volitional elimination of deep breathing (VEDB) [25].

23.3.1 Buteyko Breathing Technique Training Aspects and Hormetic Dose Response

BBT consist of concrete and structured techniques to retrain the complex involuntary mechanisms controlling our automatic breathing patterns.

Working with optimization of automatic breathing patterns, we need to take care of several aspects of the breathing physiology:

- Posture—to ensure structured posture both in rest and in motion to reduce the influence of breathing muscles from other muscle groups,
- Route—to develop breathing only through the nose both in and out, completely ceasing breathing through the mouth,
- Scope—to reduce the volume of air both in and out,

- Frequency—to reduce the number of breaths per minute,
- Velocity—to reduce the speed of the air flow both in and out,
- Timing and balance—to prolong the exhalation in relation to the inhalation,
- Rhythm—to promote even breathing flow without interruption, inhale and hold,
- Placing—to reduce the use of the breast muscles and expand the use of abdominal muscles,
- Pauses—to exercise natural breaks with relaxation after exhalation. In addition, there are many aspects of exercise that both have a strong therapeutic and preventive effect on cancer and other lifestyle diseases.

All of the aspects above can be hypothesized to trigger hormetic effects of mild stress if trained with moderation. Hormesis is an interactive process and the question is which dose will trigger the right dose response—right now, so the process of moderation in training will ultimately lead to the deliberate choice of the optimal level. Determining the right dose objectively is not easy, so we need to learn to regulate our intensity levels ourselves by heightening our ability to be sensitive, listen, and react to our body's signals while we are exercising.

23.3.2 Buteyko Breathing Technique Practical—What is Taught and What is Learned

The patient is taught the following:

- Physiology behind importance of nose breathing. Practical tips for keeping the mouth closed during both exercise and rest in a safe and effective way.
- Nose-clearing exercises requiring with a comfortable breath hold, not triggering stress response.
- The technique of measuring the current state of health/the degree of CHVS via control pause (CP) test based on comfortable breath-holding time (BHT) after normal exhalation. This test breath-holding ability relies on the observation that sick persons with CHVS have to breathe more to achieve a lower habituated $PaCO_2$ threshold, and, thus, have shorter BHT.
- Reversal of chronic hyperventilation through relaxation of the respiratory muscles that leads to reduced lung minute ventilation through and achieving a feeling of a slight shortage of air over time.
- Lifestyle changes recommended to help reducing hyperventilation. Among these are: avoid overeating, avoid overexercising, and avoid overheating.

According to Prof. Buteyko, the prerequisite for optimal BBT training is progressive relaxation during the exercise [19]. The technique of progressive active relaxation (PAR) has the potential to extend BBT into the domains of walking and running by optimizing relaxation patterns in movement. By learning relaxation in movement the trainees can retain focus on the body and high sensitivity required to not cross the threshold of light stress and ultimately harvest hormetic effects from training.

To achieve this, I use 1-pointed attention training inspired by mental techniques from internal martial arts, old Samurai legacy, and newer Ki-Aikido. Training of constant mental focus in the Hara point below the belly in combination with structured movement with right posture promotes relaxation of the diaphragm allowing for proper hormetic doses of exercise.

23.3.3 Biochemical Mechanisms of Buteyko Breathing Technique

As mentioned before, the main goal of BBT is to reverse the disease by addressing the same problems that initially triggered hyperventilation to become chronic and lead to disease. Thus, following biochemical mechanisms can be improved through optimization of breathing:

Poor oxygen extraction → Effective oxygen extraction: Studies show that our normal breath has changed significantly during the postindustrial era [26]. Textbooks in human physiology defined a normal minute ventilation as 5 L/minute (4−6 in different sources), i.e., 10 breaths of 0.5 L. Modern physiology books point at average normal minute ventilation as 6 L/minute (here conservative number is chosen out of 6−9 in different sources), i.e., 12 breaths of 0.5 L—instead of 10 breaths. All in all, 6 L/minute today against 5 L in the old medical books, a change of 1 L during the postindustrial era [19,27]. These changes are hypothesized to be caused by combination of all the sources of accumulated chronic stress detrimental for human health.

Sick persons with NCD breathe about 12−18 L/minute or about 2−3 times more than the norm. Chronic hyperventilators extract only 10% of oxygen, 90% of oxygen being exhaled back. In the severely sick it can be only 5% or less. It corresponds to 20−40 breaths per min. Healthy people have little breathing down to about 1.5−2 L/minute or only 3−4

breaths per min can extract over 50% or more of the oxygen they inhale. The maximum value of the lungs oxygen extraction is probably close to 70% [19].

Suppressed Bohr effect → Normal Bohr effect: The Bohr effect, named after the Danish physiologist Christian Bohr who described it in 1904, states that arterial hypocapnia leads to reduction of oxygen release in the tissue capillaries [28]. Hyperventilation causes hypocapnia in the lungs and arterial blood. Sick persons have suppressed Bohr effect, which leads to obstructed oxygen release, because the low absolute CO_2 concentration leads to increased oxygen affinity to hemoglobin [29]. Normal Bohr effect leads to optimized oxygen extraction rates and normal cellular oxygenation.

Cell hypoxia → Cell normoxia: Hyperventilation causes alveolar hypocapnia (CO_2 deficiency) leading to cell hypoxia (low cell-oxygen). Normal levels of tissue oxygenation and cellular O_2 levels are controlled by alveolar CO_2 and breathing. CO_2 deficiency (hypocapnia) leads to hypoxia or decreased cell-oxygen levels (the suppressed Bohr effect). The bigger lung ventilation at rest, the less the amount of oxygen is available in the cells of all the vital organs.

Arterial hypocapnia → Arterial hypercapnia/hypercarbia: Hyperventilation causes arterial hypocapnia (CO_2 deficiency) leading to cell hypoxia (low cell-oxygen). High levels of arterial CO_2 in lungs and in blood (except for hypocapnia-induced ventilation/perfusion mismatch) lead to arterial hypercapnia and better oxygenation extraction rates.

Vasoconstriction → Vasodilation and better oxygen transport: Hypocapnia constricts blood vessels (CO_2 is a potent vasodilating hormone [30] and leads to decreased perfusion of all vital organs. Hypercapnia triggers vasodilation, expansion of arteries, and arterioles.

Arteriovenous oxygen difference → Bigger a-vO_2 difference: The difference in the oxygen content of the blood between the arterial blood and the venous blood is an indication of how much oxygen is removed from the blood in capillaries related to overall blood circulation volume. It increases oxygen consumption VO_2 and reverses many health-related issues.

Spontaneous nerve excitation → Stabilized nerve excitation: CO_2 exerts sedative effects on nerve cells. Lack of CO_2 in the brain promotes spontaneous nerve excitation. "Increased neuronal excitability caused by HV-induced hypocapnia leads to spontaneous and/or asynchronous firing of cortical neurons," that can result in many mental and psychological abnormalities ranging from panic attacks and seizures to sleeping problems, addictions, depression, and schizophrenia [31].

23.3.4 Potential Hormetic Mechanisms—Buteyko Breathing Technique and CO_2

BBT has a potential to slowly normalize suppressed Bohr effect by affecting its roots by diminishing and stopping hyperventilation. Normalizing Bohr effect through BBT training is supposedly carried out through metabolic hormesis of light intermittent hypoxia and hypercapnia induced by training. Intermittent hypoxia is a fastest way to experience positive effects of hormesis through light air hunger self-induced through exercise. BBT promotes this effect through exercising diminished breathing and by some extent breath holding.

23.3.5 Buteyko Breathing Technique and Its Role in CO_2-Induced Hormesis

The biochemical effects of CO_2 on health and longevity could be considered in terms of the gas balance. The Bohr effect means that more ventilation leads to more oxygen in the lungs and in the bloodstream. In other words, the more oxygen we have in the lungs and in the blood, the less oxygen the cell receives. It sounds paradoxical as the widespread misunderstanding about carbon dioxide being nothing but waste gas has for decades promoted the biggest physiological fallacy which needs to be explained and corrected.

A study on oxidative stress and hormesis in evolutionary physiology concluded that there is scientific evidence of a potential hormetic effect in response to increased partial pressure of CO_2. This conclusion has a potential to connect all of the above-mentioned positive biochemical effects of CO_2 with hormesis [32].

23.3.5.1 Potential Hormetic Mechanisms—Buteyko Breathing Technique and Hypoxemia vs Hypoxia

Sometimes the terms hypoxia and hypoxemia are used interchangeably to address suboptimal tissue oxygenation. It is crucial to know the difference, because these two terms refer to either blood or tissue hypoxia, respectively. Hypoxemia is defined as a condition where arterial oxygen tension (PaO_2) is below normal (normal $PaO_2 = 80-100$ mmHg) [33]. Hypoxia is defined as the failure of oxygenation at the tissue level. It is not measured directly by a laboratory value

(though an increased arterial lactate level usually accompanies tissue hypoxia). Hypoxia and hypoxemia may or may not occur together. Generally, the presence of hypoxemia suggests hypoxia. However, hypoxia may not be present in patients with hypoxemia if the patient compensates for a low PaO_2 by increasing oxygen delivery. This is typically achieved by increasing cardiac output or decreasing tissue oxygen consumption. Conversely, patients who are not hypoxemic may be hypoxic if oxygen delivery to tissues is impaired or if tissues are unable to use oxygen effectively" [33]. One of the hormetic effects of BBT occur potentially through changes of blood oxygen content in the direction of hypoxemia, thus exerting hormetic dose response and promoting Bohr effect, resulting in better cellular oxygenation.

23.3.5.2 Potential Hormetic Mechanisms—Hyperbaric Oxygen Therapy vs Buteyko Breathing Technique

Dr. Buteyko could have been one of the first to suggest that hyperbaric oxygen therapy (HBOT) could have deleterious effect on the oxygen saturation in the tissue. To quote Buteyko et al. [34], "The vasoconstrictor action with an increase in the oxygen concentration in the blood can predominate over additional oxygen saturation and lead to a total decrease in the oxygen influx to the tissues, which in turn can increase the oxygen starvation of tissues in some patients, cause the above symptoms and the often negative effect of oxygen therapy. An increase in the degree of saturation of arterial blood with oxygen due to breathing with a hyperoxic mixture leads in most patients with coronary insufficiency to a narrowing of the peripheral arteries; a moderate, gradual decrease in the saturation of arterial blood with oxygen causes their dilation. Hypoxemia causes a clear dilation of arterial vessels. The consequence of hyperoxemia in some patients with hypertensive disease and coronary insufficiency are negative phenomena in the form of pain in the region of the heart, headache, dizziness, which may be associated with an increase in the tone of the arterial vessels of the respective regions. In the group of hypertensive patients, in response to hypoxemia, there was a clear dilation of large peripheral vessels."

Later studies showed that HBOT enhances the production of reactive oxygen species (ROS) and causes oxidative stress in body tissues [35]. The study about effects of HBOT on the behavior of 16 children with autism spectrum disorders concluded that: "No consistent effects were observed across any group or within any individual participant, demonstrating that HBOT was not an effective treatment for the participants in this study" [36].

It is hypothesized that the lack of effectiveness or deleterious effect of HBOT in these studies may be at least partly due to difficulty to control and tailor the grade of the tissue hyperoxemia and its hormetic effect, thus leading to the dysfunction of mitochondrial adaptive responses. BBT has a potential to exert a more perfectly graded hormetic effect here being potentiated by the increased sensitivity of the sick person during training.

23.3.6 Potential Hormetic Mechanisms—Buteyko Breathing Technique and NO

Another biochemical mechanism of BBT is through its influence on nitric oxide (NO). NO is also a potent vasodilator, while its lack causes vasoconstriction. NO is generated in sinuses and mouth breathing prevents sick persons from inhaling their own NO. NO is involved in a large number of physiological responses including bronchodilation, vasodilation, tissue permeability, immune response, oxygen transport, neurotransmission, insulin response, memory, mood, and learning [37].

23.3.6.1 Impaired NO Synthesis → Normal NO Synthesis

Basic research during the past decades showed that NO has functions as vascular smooth muscle relaxant, that nitroglycerin relaxes smooth muscle by metabolism to NO, progressing to the discovery that mammalian cells synthesize NO, and finally, the revelation that NO is a neurotransmitter mediating vasodilation in specialized vascular beds [38]. The new knowledge on NO should enable investigators in this field to develop novel and more effective therapeutic strategies for the prevention, diagnosis and treatment of numerous cardiovascular disorders. According to Ignarro [38], following biochemical functions are performed by NO:

- Neutralization of opportunistic organisms as viruses, parasites, and malignant cells in the airways and lungs by inactivating their respiratory chain enzymes.
- Regulation of coupling/release of O_2 and hemoglobin. This effect is similar to the CO_2 function in the Bohr effect.
- Vasodilation of arteries and arterioles and thus regulation of blood flow or perfusion of tissues [39].
- Inhibition/mediation of inflammatory response in blood vessels.

- Hormonal and stress regulatory effects. NO regulates hormone release in the Hypothalamic-Pituitary−Adrenal (HPA) axis and influences secretion of hormones from several glands (adrenaline, pancreatic enzymes, and gonadotropin-releasing hormone) [40].
- Neuronal signaling functions and neurotransmission. Memory, sleeping, learning, feeling pain, and many other processes are possible only with NO as neurotransmitter.

23.3.6.2 Reactive Oxygen/Nitrogen Species Free Radicals → Balanced Reactive Oxygen/Nitrogen Species Generation

Unrestrained formation of ROS takes place due to anaerobic cell respiration caused by cell hypoxia and is also regulated by CO_2 and breathing [41]. But ROS are powerful signaling molecules and our body needs them for normal cellular signaling. Simply suppressing, eliminating them indiscriminately would lead to biological dysfunction. Balancing them back to the optimal levels promotes normal signaling function.

In the CNS, NO has an array of functions, such as the regulation of synaptic plasticity, the sleep−wake cycle and hormone secretion. Particularly interesting is the role of NO as a Janus molecule in the cell death or survival mechanisms in brain cells. In fact, physiological amounts of this gas are neuroprotective, whereas higher concentrations are clearly neurotoxic [42].

Recent studies showed that reactive oxygen or nitrogen species (ROS/RNS) not only play a critical role in the initiation of diabetic cardiomyopathy, but also play an important role in physiological signaling. At low concentrations, these species may also act as second messengers, gene regulators, and/or mediators of cellular activation [43].

23.3.7 Buteyko Studies and Trials

At the moment of Dr. Buteyko's death in 2003, the list of NCD treated by BBT counted 150 diseases and conditions of deep breathing reversible by the method [19]. Effectiveness of BBT for NCDs is confirmed by an array of studies and trials with asthma, COPD, heart disease, radiation disease, and HIV-AIDS [44−46]. Here is a little selection of these trials:

- Asthma [47]. Controlled study published by The British Thoracic Society showed that the group of 360 patients was able to:
  - Reduce asthma symptoms by 98%
  - Reduce use of reliever inhalers by 98%
  - Reduce use of preventer inhalers by 92%
- Breast cancer [48]. Controlled study published in *Oncology Journal (Kiev)* showed that the group of 120 patients with metastasized breast cancer was able to:
  - Reduce 3-year mortality fivefold in relation to the control group
- Hepatitis B and liver cirrhosis [49]. Controlled study at The Institute of Epidemiology and Infectious diseases (Kiev) showed that the group of 30 patients, diagnosed with acute (6 patients) and chronic (18 patients) hepatitis and cirrhosis of the liver (6 patients) was able to:
  - Show remissions of symptoms in 28 patients
  - Show improvements in blood test results for 25 patients
  - The official documents report 93% success rate
- Chronic fatigue syndrome (CFS) [45]. Study by Shellie Gaskin at Perth Academy of Natural Therapies, Australia, was conducted in 1997 on 15 people diagnosed with CFS. There were following improvements:
  - fatigue 87%, night sweats 75%, depression 70%, allergies 66%, anxiety 66%, muscular aches 60%, difficulty sleeping 54%, and headaches 50%
  - After 10−12 weeks all those who continued their breathing exercise regimes reported a 100% reduction in fatigue.

23.3.8 Other Nonpharmacological Metabolic Approaches for Breathing Optimization

As mentioned before there are several approaches to breathing exercises. BBT combines the following:

- Hypoxic exercises
- Hypercapnic (hypercarbic) exercises
- Breathing techniques based on the reduction of the rate of breathing
- Breathing techniques for reduction of minute ventilation/breathing volume

There are other approaches for breathing exercises that could support and extend the BBT training regimen further. These approaches consist of:

- Exercises using additional breathing space (ABS)
- Breathing exercises with breath resistance

My experience (unpublished observations) as among the most efficient devices combining the two exercising approaches are: Frolov device [50], DIY breathing device [51], and elevation training mask [52]. Exercise with ABS increases the resistance of the body to oxygen and carbon dioxide fluctuations by effectively increasing dead volume as the key factor. It provides for bigger rebreathing rate of exhaled CO_2 thus stimulating the adaptation to hypercapnia and hypoxia. Dead volumes are as follows:

- Mouth breathing (dysfunctional)—100 ml
- Nose breathing—150−200 ml
- Frolov device—350−400 ml (incl. nasal cavity)
- Elevation mask—400−450 ml (incl. nasal cavity)
- DIY device by Dr. Rakhimov—200−700 ml (incl. nasal cavity)

Exercise with breath resistance trains the respiratory muscles, which results in better lung ventilation, strength and stamina of the respiratory muscles. By enabling the diaphragm muscle, it also provides for gentle massage of internal organs promoting better lymph drain upwards from the internal organs, since about 60% of all lymph nodes in the human body are located under the diaphragm [19]. Both approaches enhance adaptation of the respiratory center to higher CO_2 with slower and lighter breathing at rest which leads to improved oxygen transport with hypercapnic vasodilation, improved Bohr effect and higher VO_2max.

All the devices can be used with advantage in parallel with Buteyko training. The progress on both device-based NPMA approaches can be measured using CP body-oxygen test (BOT).

23.3.9 Buteyko Breathing Technique Measurement Strategies, Control Pause or Breath-Holding Time

In all training, it is important to have some guidelines in order to measure progress. BBT provides us with such an indicative parameter to measure. CP or BOT reflects the normality of the regulation of gas balance in the lungs, as well as the blood and body pH and thus reflects the level of disease. The CP can be measured with a stopwatch. It constitutes time of a breath-hold performed after a normal effortless exhalation and until the first urge to breathe that closely correlates and followed up by involuntary reflexive muscle contractions of swallowing and a first light movement of diaphragm.

The default value for normal CP is 40 seconds. Dr. Buteyko's clinical experience has shown that a CP over 60 seconds is incompatible with a list of 150 NCD incl. cancers [19,44−46]. When CP is measured in the morning, it is called MCP, the most important parameter for assessing both health condition and sleep efficiency. A structured therapeutic NPMA strategy supports the sick persons in expanding their individual CP from 5 to 10 seconds (which is common for NCD) to over 60 seconds. As a health practitioner, I have experienced several of my clients achieving MCP in over 120 seconds that belong to super health according to Buteyko table of health zones.

It is crucial to note that the trends in CP development during the NPMA process reflect the normalization of the whole body metabolism, including development of the current inflammatory status and allostatic resilience. Thus, CP can be proposed as a major universal measurement strategy for NPMA.

23.4 KETOGENIC REGIMEN AS STRATEGIC NONPHARMACOLOGICAL METABOLIC APPROACHES FOR OPTIMIZATION OF NUTRITION AND ITS HORMETIC EFFECTS

KD regimen as a WOE has been used as a therapy against epilepsy for almost 100 years [53]. It is known as high-fat, moderate-protein, and very-low-carbohydrate KD, which is more a WOE than a diet because the state of ketosis is physiological rather than a pathological condition. All babies before weaning are in ketosis, just like many indigenous populations stayed in ketosis for the most of their life according to different anthropological studies [54]. Already in 1863 in his book "Letter on Corpulence," William Banting described his own successful treatment of obesity with a low-carbohydrate diet [55]. KD was used since the 1920s to treat childhood epilepsy and was also known to help type 2 diabetics to achieve normal blood glucose levels without medication [56].

The last decades of demonization of dietary fats was kick-started by a study of Ancel Keys that led to formulation of dietary lipid hypothesis [57]. Despite an abundance of anecdotal evidence and scientific research on the therapeutic advantages of KD, there is still flourishing myths about it as being unsustainable and unsafe. Several aspects promote this situation, such as persistent propaganda of low fat [58], lack of nutritional training in medical educational programs, overreliance on pharmacotherapy in choice of scientific research topics, and lack of practical tools to promote education and lifestyle change for the sick persons.

The situation is about to change now after a significant increase in research on KDs, the major shift in opinion regarding dietary fat is emerging that leads to comeback of KD [59]. Today there is a vast array of studies on therapeutic effects of KD in a number of NCD and disorders, as cardiovascular disease, diabetes, obesity, cancer, and neurodegenerative conditions such as Alzheimer's and Parkinson's disease.

23.4.1 What Is Ketogenic Diet?

In this chapter we are talking about synergetic effects of combination of optimization of breathing and nutrition. As mentioned before, the chemical energy ATP is formed in the human cells as product of respiration to oxidize common nutrients (sugar, amino acids, and fatty acids) with the most common oxidizing agent (oxygen). Therefore, it could be reasonable and logical to look at KD from the perspective of oxidation.

For the purpose of simplification, one could say that there are two main sources of fuel for the majority of cellular functions—glucose or fatty acids. Both sources of fuel can be used for cellular respiration— energy production in presence of oxygen. In case of glucose, cellular respiration can only store only around 2.500 kcal in form of glycogen in the liver and in the muscle tissue. Any excess glucose beyond that is converted via lipogenesis and stored in adipose tissue as fat. The whole body's glycogen stores last only for about 1−2 hours of intense exercise. In case of fat, cellular respiration can be fueled through fat stored in adipose tissue, which is available in abundance of at least 40.000 kcal in the most lean individuals [60]. Fat as fuel supply includes both fatty acids and ketone bodies, a metabolite from the breakdown of fatty acids in the liver. Compared to scarce energy availability of high-carb diets with depletion after only 1−2 hours of exercise, the whole body's fat stores can last for at least several days of exercise.

Ketogenic initiation: Around 1−2 days after the shift to the KD WOE the body's glucose and glycogen stores become depleted. Generally, in order to initiate the ketosis carbohydrate consumption must be between 0 and 50 g/day with moderate protein consumption (between 0.6 and 1.0 g of protein per kg lean body mass) to avoid excessive gluconeogenesis (GNG) in the liver [60]. That is where the shift toward the state of ketosis occurs, where the stored and/or dietary fat in form of fatty acids and ketones is being used as preferred source of energy— instead of glucose.

Ketogenic adaptation: After the initial shift into ketotic state the period of ketogenic adaptation begins where the mitochondrial enzymes become slowly optimized for using fat as preferred source of fuel. Ketogenic adaptation includes several stages of gradual optimization of ATP flow and rates of fat oxidation up to 10 times from 10 to 110 g/hour [61]. On high-carb diets, high insulin being a power inhibitor of lipolysis suppress fat metabolism resulting in the body's inability to effectively use its own fat reserves. As a result, the blood levels of ketones are very low, about 0−0.3 mmol/L. After a transition to ketosis, the body relies on ketones as the main energy source for the brain and heart, as well as during mild, moderate, and even intensive exercise (for later stages of keto-adaptation). As a result, the blood levels of ketones are higher than 0.5 mmol/L, which is a threshold for nutritional ketosis and up to 5.0 mmol/L [60].

Hunger regulation in KD: Normally the hunger levels are influenced by glucose levels, but after the initial ketogenic adaptation period the hunger becomes mainly influenced by the energy levels. It is a common experience that the levels of leptin and ghrelin are slowly normalized during ketogenic adaptation and the general need for food is slowly decreased, so it becomes normal to eat only twice a day because of stable satiety and energy levels. Here it is crucial to include eating organ meats as liver, bone marrow, heart, and kidney in order to maintain healthy levels of micronutrients as vitamins and minerals [60].

23.4.2 Biochemical Mechanisms of Ketogenic Diet and Its Physiological and Metabolic Benefits

There is a large body of scientific studies showing that KD as a powerful NPMA regimen can handle all the four metabolic risk factors for NCDs and MetS mentioned previously in this chapter [62−65].

A primary application of KD is in the management of insulin resistance, which is the hallmark and the primary defect of MetS [18]. In connection to high-carb diets, insulin resistance is associated with impaired carbohydrate

metabolism. Thus, insulin resistance is characterized by impaired carbohydrate metabolism that can be effectively managed by restricting dietary carbohydrate with KD regimen. What follows is a brief overview of KD from the biochemical point of view and explore its biochemical mechanism and potential hormetic effects.

KD and aging: Aging is associated with elevated levels of glucose, insulin, and triglycerides. Nutritional program including KD regimen can reduce these correlates of aging and lead to improvements in serum factors related to the aging process as body weight, fasting serum glucose, insulin, leptin, lipids, and thyroid hormone [63].

Inflammatory markers: Comparison of 14 different inflammatory markers made for low-fat and low-carbohydrate diets showed all of them being lower for low-carbohydrate diet [65]. These authors concluded that a very low-carbohydrate diet resulted in profound alterations in fatty acid composition and reduced inflammation compared to a low-fat diet.

Normalized ROS and oxidative stress: Several other studies discovered that, for diets based on carbohydrates, the degree of oxidative stress and generation of ROS relates to and/or was proportional to increases in blood sugar and blood insulin levels. [66–68]. Ketones prevent a dysregulated ROS production with less oxidative stress than glucose molecules, when used for fuel in the mitochondria [64]. Ketone bodies also provide protective effects for mitochondria, reduce oxidative stress in the brain and blood levels of free radicals [69].

23.4.3 Fasting as a Tool for Health and Longevity and a Precursor to the Ketogenic Diet

Different kinds of dietary restriction (DR) such as fasting and caloric restriction (CR) are relatively well researched as regimens leading to better health and longevity and may effectively modulate several disease risk factors [70]. But DR has many challenges in our modern environment because of high food availability being one of the main ones. In modern an economically rich countries food is omnipresent all the time, and it requires tremendous effort of self-control to restrict feeding. However, hunger-reduction phenomenon reported during KD is well known [62]. Thus, adaptation to a ketogenic regimen can serve as an appropriate platform to harvest benefits from fasting and CR, as it diminishes suffering from hunger substantially. Keto-adaptation has been shown to be a good tactic to normalize balance and regulation of hunger and satiety hormones leptin and ghrelin and thus suppress appetite [71].

One of the first demonstrations of hormetic effects of CR on longevity was a 1934 study of calorie restriction that found that reducing the calories of rats by 30–50%, supplemented with adequate micronutrients, could almost double their life spans [72]. Other studies showed life span extension with CR up to 65%. In addition, the rats remained energetic and youthful in appearance, with greatly reduced incidence and delayed onset of age-related diseases. Studies conclude that CR is indeed a daily, long-term, repeated, low-intensity stressor and thus a strong hormetin [73].

It can be hypothesized that CR is much easier to implement in KD than on other dietary regimens because of normalized insulin response, improved leptin–ghrelin balance and better sustained satiety. Another modification of ketogenic regimen is calorie-restricted KD (CRKD) which is an effective therapeutic approach based on the principles of evolutionary biology and metabolic control theory [74].

23.5 SYNERGETIC HORMETIC EFFECTS FOR HEALTH AND LONGEVITY FROM COMBINED USE OF BUTEYKO AND KETOGENIC REGIMENS

In this chapter, I will suggest the metabolic and hormetic effects of the combined use of these two therapeutic approaches—as the art of connecting the dots. While there is an array of studies showing effectiveness of both BBT and KD for lifestyle diseases as different types of cancers, asthma, diabetes mellitus, neurodegenerative, and cardiovascular diseases [9,47,48,75], there are no studies to date showing the synergetic effects of their combined uses. KD and BBT can create a powerful synergetic effect when used simultaneously as a part of the same NPMA program with following aspects:

Reversing insulin resistance and mitochondrial respiration: Studies show that insulin resistance leads to reduced mitochondrial oxidative function, increased reliance on anaerobic metabolism, and impaired ability to respond to conditions of maximal respiratory demand. These defects contribute to not only impaired energy homeostasis, but also increase oxidative stress [76]. Ketogenic low-carb adaptation has several stages. Studies show that fat-burning ability

increases with time for persons following ketogenic regimen [60]. Once body cells are adapted to fat and ketones as the preferred energy source, two things change that influence the respiratory drive:

1. Lower respiratory quotient (RQ) for the most workloads. Diminished from 1.0 (carb burning) to 0.7 (fat burning). RQ is the ratio of expired CO_2 to consumed O_2. Burning carbs results in equal amounts of CO_2 and O_2, hence RQ = 1.0. Burning fat results in 70% as much CO_2 expired compared to glucose, hence RQ = 0.7 or close, depending on the nutritional macronutrient distribution and load [77]. Practical applications of RQ can be found in COPD, in which patients spend a significant amount of energy on respiratory effort. In KD the RQ is driven down, causing a relative decrease in the amount of CO_2 produced, thus reducing the respiratory burden to eliminate CO_2. This reduces the amount of energy spent on respirations.
2. Lower lactate levels: there is less lactate production in any workload following the enhanced ability to oxidize lipid associated with keto-adaptation. Under most circumstances one is protected from intense sense of "air hunger" that comes from lower blood pH.

Both lower RQ and lower lactate are promoting synergetic effect from breathing retraining, extending BHT and leading to calming effect of NFbL.

Keto-adaptation promotes high-fat oxidation rates: Long-term keto-adaptation results in extraordinarily high rates of fat oxidation, whereas muscle glycogen utilization and repletion patterns are similar. The average contribution of fat during exercise in the low-carb and high-carb groups were 88% and 56%, respectively, with stable and higher fat oxidation rates of $\sim$ 1.2 g/minute in the low-carb group, whereas fat oxidation values were significantly lower in the HC group at all time points [78].

Ketogenic adaptation and better use of oxygen: More energy is derived per oxygen molecule with ketone metabolism [77]. Oxygen utilization advantage is moving many elite athletes toward transition to KD. This also helps performance at high altitudes. Studies show that KD protects against hypoxia, improving the ability to function and survival advantage at extreme altitude, resulting in ability to remain unimpaired while breathing much lower percentages of oxygen [79].

Ketones as preferred fuel for the brain cells: Fat is a very energy-dense fuel providing 9 kcal/g compared with 4 kcal/g from carbohydrate. But the efficiency of using fat for fuel is not only about calories. Our brain's intellectual capacity is not only related to increased size but also strongly correlated with enhanced blood flow and efficiency in use of oxygen. Studies indicate that cerebral blood flow (CBF) increased at an unexpectedly rapid pace over a period of three million years and our brains are six times as hungry for oxygen as those of our ancestors with blood flow rates increased from about 1.2 mL/second to 7 mL/second [80]. This would suggest that the most important fuel for the brain is going to be one that uses oxygen more efficiently and this is exactly what ketones do. Administering ketone bodies to a rat heart led to a 25% increase in hydraulic work but a decrease in oxygen consumption [81] which was explained by the increase of the efficiency of energy production in the cells mitochondria by the ketone body BOHB (ß-hydroxybutyrate).

Studies suggest an increase in the metabolic efficiency of human brain using ketoacids as their principal energy source instead of glucose [81]. People who have done extended fasts often report an enhanced mental state of clarity between day 5 and 7 when ketone bodies have reached a particularly high concentration over 5 mmol/L [82].

Vasodilatory effects of ketones, CO_2, and NO: Ketone bodies create a powerful synergetic effect with blood gases optimizing dilation of blood vessels. CO_2 and NO are known vasodilators. Ketone bodies are also able to increase global CBF by 39% [83] at blood ketone levels characteristic of the state of ketosis. These observations indicate that the mechanism responsible for the increase in CBF is rather a direct effect on the cerebral endothelium than via some metabolic interactions [84].

Ketosis promotes easier breathing practice: KD and the state of ketosis open up for easier planning of BBT practices. To make progress on BBT needs daily exercise. It is normally recommended not to perform breathing exercises close to meals. People on KD often make transition from, e.g., 5−2 daily meals because of greater satiety [60]. Besides breathing exercises can be planned much easier during the day if the meals can be skipped or moved because of down-regulated hunger and more lasting satiety.

Reduced total digestion time and smaller CP drop after meals: In comparison with high-carb diets KD reduces total time required for digestion per day because of higher satiety throughout the day with the resulting fewer number of meals [60]. Control pause drops after meals because of slightly heavier breathing under digestion and peristaltic movements. KD causes smaller CP drop in comparison with high-carb diets increasing average daily CP value. This leads to easier breathing and a better progress through cumulative effect promoting higher CP next morning.

More stable mood throughout the day: Frequent fluctuations of blood glucose levels characteristic of high-carb diets, lead to fluctuations in mental clarity, mind state, and other neurological and psychological parameters. Ketosis flattens these fluctuations resulting in more stable mood throughout the day [60].

Bohr effect the strongest hormetin promoted by ketosis: The Bohr effect explains how BBT training gradually changes the threshold of CO_2 sensitivity in the breathing center situated in medulla oblongata. This happens by low-grade stress oscillation through exercise induced intermittent hypoxia. The continuous perceived air hunger is tolerated better with exercise as medulla oblongata is conditioned for higher alveolar CO_2 levels. This process is promoted synergistically by KD and CR or intermittent fasting (IF) through lower RQ and lactate levels, better energy through ketogenic adaptation with higher fat oxidation rate, vasodilatory effect of ketones, and diminished peristaltic movements.

Optimized sleep and dawn effect: Optimization of breathing raises CP and lowers the pulse. It is of great importance that morning pulse is consistently lower than the evening pulse as it shows absence of nightly hyperventilation. The pulse lowers during the night only if sleep is improved with normalized breathing pattern [19]. Good sleep is also promoted by KD and CR/IF through the positive effects mentioned earlier. Absence of gut movement is especially crucial leading to more effective autophagy, as well as shorter nutritional window as a direct consequence of more stable and lasting satiety. Activation of CMA autophagy is associated with nutrient deprivation and starts more than 10 hours into the starvation process, reaching the plateau of maximal activation after 36 hours following the onset of starvation [85].

Optimized breathing and nutrition leads to optimized sleep with prolonged deep sleep stages. This in turn results in diminished need for sleep and shorter overall sleep duration. BBT practice shows that during training people experience shorter sleeping time, waking up naturally earlier in the morning. High CPs around 60 seconds correlate often with diminished need for sleep (around 5 hours) with full restitution and daytime alertness [19].

Early waking hours can be further promoting health through minimizing chronic morning rebound hyperglycemia also called Somogyi effect [86] or dawn effect, where early morning hormonal changes (high morning cortisol and insulin) cease their deleterious effect on blood pressure and breathing, stopping hyperventilation and allowing CP to accumulate. It is suggested that the hyperglycemia attributed to the Somogyi effect actually is caused by insulin resistance [87].

There is a distinction between Somogyi effect and dawn effect, where the first occurs in the case of excessive amounts of exogenous insulin and the second when endogenous insulin secretion decreases together with a physiological increase in insulin-antagonistic hormones [88]. Both effects are detrimental to health and can be effectively approached by lifestyle change to stop and reverse the endless cycle of insulin resistance.

According to many professionals working in palliative care, the most of the deaths happen during early morning hours. This fact was also described by Buteyko who was actively promoting conditioning to earlier waking hours through optimization of breathing and lifestyle change, including different aspects of sleep hacking.

No soiling effect—healed gut inflammation: One of the strong indirect indicators of synergetic metabolic effects directly influenced by BBT and KD regimens is healing of chronic gut lining inflammation, which is one of the most common symptoms of MetS. This chronic inflammation is often called leaky gut as a consequence of increased permeability of intestinal wall. When the inflammation is healed the person often experience a so-called "no soiling effect," where there is no longer need to use toilet paper as it remains unstained after use. This effect of normalized gut health is lasting and is often seen as a direct consequence of breathing normalization [89].

23.6 A UNIVERSAL TRAINING PROTOCOL AS NONPHARMACOLOGICAL METABOLIC APPROACHES STRATEGY FOR HEALTH AND LONGEVITY

I propose a universal protocol for health and resilience (UPHR) that integrates several basic areas of human health into one structured process of training and lifestyle change.

The idea behind UPHR is to visualize and map the connection between the cellular and the human environment in order to open up for measurable effects on health and resilience through training and lifestyle change.

The theory of "dynamic reciprocity" [90] proposes that the cellular microenvironment in form of the extracellular matrix (ECM) exerts physical and biochemical influences on a cell, which ultimately effect changes in gene expression in the nucleus. Latest research on metabolic origins of lifestyle diseases further confirms the critical role of the microenvironment in regulation of genetic expression and cellular health [9,75].

It is hypothesized that the basic areas of cellular microenvironment can be optimized through structured training and lifestyle change where the five basic areas of practical training (human macroenvironment) are structured to fit five basic areas of cellular health (cellular microenvironment, ECM). Fig. 23.1 presents a mapping of dependencies in the connection between the human and the cellular environment.

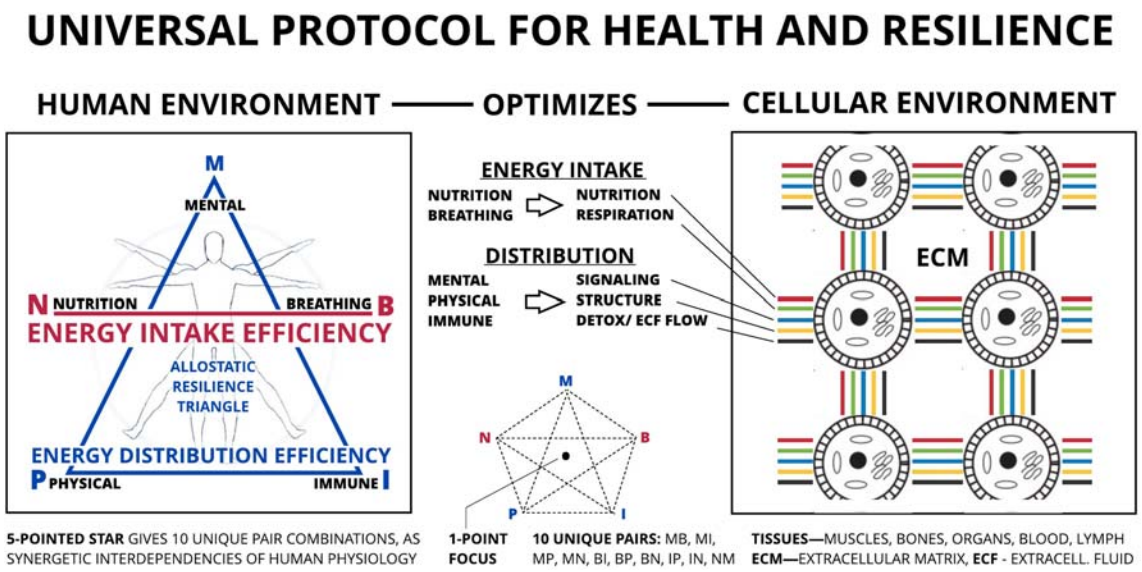

FIGURE 23.1 UPHR—mapping of dependencies in the connection between the human and the cellular environment (ECM).

23.6.1 Components of Universal Protocol for Health and Resilience

Looking at the human environment we can identify several basic areas of practical training and lifestyle change, that can be divided into two groups, as follows:

- Energy intake— energy acquired from the environment
- Energy distribution— energy utilized by the body

Energy intake: Energy acquisition from the environment can be optimized through fields of breathing and nutrition.

Energy distribution: Energy distribution and utilization by the body can be optimized through training of allostatic resilience to minimize energy loss—the difference between acquired and utilized energy. The effectiveness and allostatic resilience can be viewed as the ratio of Q (energy output) to W (energy input), called performance coefficient (CoP) [91].

UPHR and NPMA in general can optimize energy utilization and CoP through structured training and lifestyle change, thus minimizing energy loss and increasing systemic efficiency: $CoP = Q/W \rightarrow 1$.

Energy intake—basic areas subdivision: Energy intake can be subdivided into two basic areas of practical training and lifestyle change as follows:

- Nutrition
- Breathing

Nutrition

Optimization of nutrition has a direct effect on digestion of nutrients through the digestive system and absorption by the cell. Tools used in UPHR combine restricted ketogenic diet (CRKD) with fasting, both IF and extended water fasts (2−7 days).

Breathing

Optimization of breathing has a direct effect on mitochondrial respiration. Tools used in UPHR to optimize automatic breathing patterns combine BBT with breathing devices mentioned previously in this chapter.

Energy distribution—basic areas subdivision: Allostatic resilience triangle

Energy distribution can be subdivided into three basic areas of practical training and lifestyle change as follows:

- Mental
- Physical
- Immune

Resilience in general affects ability to return to high utility state following perturbations [92]. It is hypothesized that resilience in humans can be enhanced through training of its three parts—mental, physical, and immune. In UPHR this is called “allostatic resilience triangle” (Fig. 23.1).

The proper elaborate mapping of different aspects of allostatic resilience in the human and the cellular environment could be a task of a separate study, so I will try to explain it in short here.

Mental resilience

In the human environment, mental resilience is a part of allostatic resilience that reflects the ability of the body to withstand psychological stressors and adapt to life tasks, maintaining normal hormonal balance and neuroendocrine signaling [93]. To optimize mental resilience, UPHR uses training of relaxation patterns through PAR in combination with training of 1-pointed attention.

In the cellular environment, it is hypothesized that this resilience corresponds to the ability by the ECM to maintain proper signaling function by the cell.

Physical resilience

In the human environment, physical resilience is a part of allostatic resilience that reflects the ability of the body to withstand, adapt, and recover from physical load and stressors. To optimize physical resilience, UPHR uses multipurpose training inspired by Dharma-Marga and Tibetan yoga, forefoot walking, jogging, bodyweight exercise, as well as kettlebell and clubbell training.

In the cellular environment, it is hypothesized that this resilience corresponds to the ability by the ECM to maintain proper structural and adhesive support function by the cell mediated through the interstitial matrix and connective tissue [94].

Immune resilience

In the human environment, immune resilience is a part of allostatic resilience that reflects the ability of the body to withstand, adapt, and recover from opportunistic organisms and pathogens as bacteria, viruses, fungi, or protozoa. Among techniques used in UPHR to optimize immune resilience are forefoot walking/ jogging, 3D multipurpose exercise to promote in-movement lymph drain, as well as different types of cold exposure.

In the cellular environment, it is hypothesized that this resilience corresponds to the ability by the ECM to maintain proper flow, viscosity, and composition of extracellular fluid (ECF) as well as blood and plasma.

1-point focus and kaizen

All the five basic areas of practical training and lifestyle change are exercised interdependently through 1-pointed focus with PAR. This contributes to optimized energy utilization and performance coefficient $CoP = Q/W \rightarrow 1$, minimizing energy loss. Kaizen process philosophy is used to establish strong practical approach to process implementation into small daily routines [95].

23.6.2 Success Criteria and Measurement for Universal Protocol for Health and Resilience

Success criteria as well as measurement in NPMA depend on the actual application and can vary depending on the disease or condition. Measurements can include both traditionally used in conventional medicine for specific diseases as, e.g., leukocyte count in leukemia or specific serum tumor markers for different cancers, as well as NPMA-specific measurements. The following measurements can be used universally in NPMA and are gender neutral:

Control pause

The most vital breathing parameter in BBT is morning CP. BBT establishes the CP of 60 seconds as a major success criterion for all chronic reversal of all chronic lifestyle diseases [19]. Control pause measurement includes:

- Morning CP (MCP), seconds
- Evening CP (ECP), seconds
- Nightly CP change, $CP_{\Delta} = MCP - ECP$
  - Positive CP_{Δ} shows improvement of sleep quality, $MCP - ECP > 0$
  - Negative CP_{Δ} shows decrease of sleep quality, $MCP - ECP < 0$
  - Maximum CP (CP_{max}), seconds

Glucose/ketone ratio

Blood parameters consist of morning ketone and glucose levels and their combination called G/K ratio [96]. Adjusting this ratio around 1 is one of the major success criteria with TKD IF/CR dietary work. The ratio between 1 and 10 can be used for different applications, depending on the severity of condition and the stage, from highly therapeutic (≤ 1) to maintenance (5−10). G/K ratio measurement consists of:

- Serum glucose (mmol/L or mg/dL)
- Serum ketones (mmol/L or mg/dL)

Triglycerides/ HDL cholesterol ratio

The study from 2017 concluded that TG/HDL-C ratio can be considered as a strong reference criterion of MetS and low insulin sensitivity in healthy adults [97]. This measurement consists of:

- Triglycerides (mmol/L or mg/dL)
- HDL cholesterol (mmol/L or mg/dL)

If lipid values are expressed as mg/dL, then the TG/HDL-C < 2 is normal and TG/HDL-C < 1 is ideal. If the lipid values are expressed as mmol/L, these threshold ratios should be multiplied by a factor of 0.4366.

23.7 FUTURE PERSPECTIVES

In this connection many questions of great importance arise. They need to be answered in order to design strong therapeutic strategies for metabolic cures or prevention of lifestyle diseases. Understanding how to seamlessly combine and integrate the different areas of health will promote the use of truly noninvasive, drug-free multifactorial approaches capable to trigger synergetic effects of healing.

Paradigm shift—education instead of medication: I hope that the paradigm shift will come one day where the industry will make a slow shift toward education—instead of medication. Moving from sick care to health care and toward noninvasive metabolic therapies—instead of constantly finding new genetic pathways to create new highly invasive chemical drugs. One day the industry will empower us to enjoy our right to take responsibility for our health back into our own hands—through education.

NPMA challenges—more than one variable: One of the big challenges for the NPMA is that the conventional way of making science refuses to encompass scientific trials with more than one variable. But when the disease is multifactorial it has a variety of variables that need to be addressed. The scientists are used to make trials with one pill against a no pill in a placebo group. But the disease cannot be cured by one pill, because it depends on multiple lifestyle factors.

Epigenetics, stress, and hormesis—the uneasy art of moderation: Our growing understanding of epigenetics suggests that multiple stress factors, including mental, physical, immune, nutritional, and environmental factors, can awaken the sleeping genes. In our busy times and society many of these factors often combine through our lifestyle, becoming chronic disease. This can further amplify their effect, making it even more likely to trigger the genetic expression [98]. How can we diminish the impact of negative stress factors? Firstly, by affecting them directly through change of lifestyle and behavior. Secondly, by changing our perception of the environment and actively transforming never-ending chronic stress into limited finite acute stress. The latter is of great significance for management of MetS in the light of NPMA as it allows for healing through diminishing the allostatic overload [93,99].

Need for paradigm shift from target-oriented toward process-oriented work: The change toward moderation for health and longevity will allow to diminish allostatic overload and avoid overtraining syndrome in all of the training regimens, as physical movement, breathing, nutrition, and lifestyle change [100]. As an example from the domain of physical training, the change toward process orientation will shift measurement strategies away from usual distance, time, speed, intensity, number of repetitions toward the depth of relaxation in movement. In this connection, the PAR concept can improve sensitivity and thus promote positive effects of hormesis in practice.

In a bigger perspective we need a paradigm shift from target-oriented toward process-oriented work and training structures.

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