

# Homeostatic Apoptosis and Allostatic Apoptosis

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## ABSTRACT

Genetics and Epigenetics are the integral parts of homeostasis. But it remains unrealistic to assess the health or disease status of the individuals at the genetic or epigenetic level. Fortunately, numerous variables related to homeostasis and allostasis are measurable genetic expressions (phenotypes), thus we are relying primarily on vital signs, somatotype, exercise performance, quantifiable biomarkers, etc., without investigating the exact favorable and unfavorable epigenetics. In view of the aggravating uncertainties created by asymptomatic and symptomatic transmission of infections, an immunological classification system (preferably based on ‘Exercise Tolerance Diversity’) should be discovered as it becomes necessary to quantitatively measure the immunologic strengths of humans in all the phases of life cycle. In fact, large amounts of literatures reveal apoptosis as one of the crucial cellular mechanisms that can either promote or ruin the health of humans. No organ or specialized cell or physiologic process in the body operates on its own, thus apoptosis also must happen in response to homeostatic fluctuations. Both health and disease operate on a multifactorial background. Though the data is limited, the empirical evidences show recurrent illness history among the individuals who undergo structured exercises associated with significant improvements as compared to their baseline exercise tolerance standards. Meticulous homeostatic apoptosis can be expected if exercises are supported by appropriate healthy lifestyle. In contrary, erroneous allostatic apoptosis is inevitable if exercises are unsupported by appropriate healthy lifestyle. Thus, in combination with ‘health risk habits’, both sedentary and overtraining conditions can elevate the allostatic

load and disrupt the optimal apoptotic regulation of the body. Elevation of allostatic load and morbidities can also be caused by psychological issues (exercise addiction, anorexia nervosa/bulimia), and in general, among all those who excessively or solely depend on pharmaceutical interventions associated with reluctance or ignorance to rectify the impediments in lifestyle. At the cellular level, the enjoyability and productivity of human life depends on durable homeostatic stability regulated by faultless apoptosis. This article aims at critically analyzing apoptosis and lifestyle.

**Keywords:** Apoptosis, Lifestyle medicine, Immunology, Epigenetics, Exercise, Homeostasis, Allostasis

## INTRODUCTION

Life cycle of humans is mysterious, and throughout an unpredictable lifespan, each individual encounters multiple types of stimuli or stressors favoring health and diseases. Even if all the necessary sources for subsistence are provided in all the phases of the life cycle, there would still be perilous perturbations in homeostasis, increased allostatic load, health instability and mortality risks in human life due to lifestyle behaviors and inadequate knowledge about health. The processes involving the human life cycle are influenced by genetic, biological, psychological and sociocultural aspects.<sup>[1]</sup> “Health stability is directly proportional to homeostatic stability. Homeostasis at rest and during exercise are mutually dependent/benefitting physiology. Health and disease depend on the equilibrium and

imbalance, respectively, in this mutually dependent physiology. A single objective measure of homeostasis based on exercise tolerance will suffice to understand a person's immunocompetence, resistance to diseases, prospective ageing trajectory, recovery from any illness, etc.,<sup>[2]</sup> "Essentially all organs and tissues of the body perform functions that help maintain nearly constant conditions in the internal environment. Physiologists call this high level of internal bodily control *homeostasis*. Each cell benefits from homeostasis, and in turn, each cell contributes its share toward the maintenance of homeostasis. This reciprocal interplay provides continuous automaticity of the body until one or more functional systems lose their ability to contribute their share of function. When this happens, all the cells of the body suffer. In disease states, functional balances are often seriously disturbed and homeostasis is impaired. Extreme dysfunction leads to death; moderate dysfunction leads to sickness. Thus, when even a single disturbance reaches a limit, the whole body can no longer live".<sup>[3]</sup> Allostatic load is the long-term result of failed adaptation or allostasis, resulting in pathology and chronic illness, caused by failure of adaptation process of the complex physiological system to physical, psychosocial and environmental challenges or stress.<sup>[4]</sup> Sometimes very surprisingly, exercisers who put substantial efforts to stay healthy also fall sick (or even acquire life threatening medical conditions) and their sickness characteristics might not even differ from the sedentary individuals with higher allostatic load. "Overtraining Syndrome (OTS) reflects the unsuccessful attempt of the body to cope with the physiological and psychological stress of exercise training and life - the total allostatic load and resultant wear and tear on the body from chronic stress. Decreased physical performance, increased incidence of infections, decreased maximal lactate response to exercise, amenorrhea in women, hypogonadism in men, loss of competitive

desire, weight loss, disturbed sleep, fatiguability are some common features of hyperarousal OTS and hypoarousal OTS".<sup>[5]</sup> Exercises can render both prophylactic and therapeutic stimuli, and are well-known to be the predominant non-pharmacological strategy to enhance the homeostatic stability and survival athleticism. Evidence based practice shows that even the individuals who undergo structured exercise participation accompanied by consistent progress in their fitness standards also acquire illnesses chiefly fever, cold, nasal congestion, cough and fatigue. Of late, such illnesses are also viewed as an infectious disease transmitted by some known or unknown person(s). Sometimes individuals with high athletic potential suspect or accuse any unhealthy non-athletic person for acquisition of such illnesses. Conversely, unhealthy non-athletic persons also suspect or accuse any healthy athletic person if they acquire any illnesses. Both are illogical because both these groups immeasurably differ in their immunologic strengths. Apart from this, the healthy asymptomatic individuals fearful about acquiring infectious disease from other healthy asymptomatic individuals is also one of the latest prevalent phenomena in the globe. "Hypochondriasis (HC) involves preoccupation with fears of having a serious medical illness based on the misinterpretation of benign bodily perturbations. Individuals with HC also perform behaviors such as checking and reassurance-seeking presumably to reduce health-related fears".<sup>[6]</sup> Human diversity is enriched with immune-diversity though we lack a feasible objective test to grade the immunologic strengths of the individuals to acknowledge this immune-diversity. Immune-diversity correlates with 'Exercise tolerance diversity', probably enable identification of a broad spectrum of people if an objective immunological classification system is discovered. Such immunological classification system is plausible based on the measurement of exercise capacity of the individuals. "Less work capacity in a given

time period, Low resistance to fatigue and Slower recovery from fatigue are the foundations of homeostatic instability and unsuccessful aging, and conversely, More work capacity in a given time period, High resistance to fatigue and Quicker recovery from fatigue are the foundations of homeostatic stability and successful aging”.<sup>[7]</sup> By incorporating salutary lifestyle components, unhealthy people will be able to transform and build the core characteristics of homeostatic stability and successful aging. On the other hand, if the salutary lifestyle components are deteriorated, healthy people will eventually acquire the core characteristics of homeostatic instability and unsuccessful aging. Therefore, indomitable perseverance and cutting-edge scientific approaches are needed to avoid/tolerate illnesses and allostatic load. Unresolvable immunologic puzzles can be tackled through interpretation of health and diseases based on apoptosis. Both sedentary life and active life can influence apoptosis. Experiential findings show that the exercises are unable to exert ‘antidote effect’ against malnutrition, disordered sleeping habits, alcoholism, smoking, adverse effects of pharmaceutical products, etc., which means if an individual decides to exercise, he/she should be proactive in regulating or bridling all other lifestyle components conducive enough to (i) obtain the complete range of benefits of exercises and (ii) prevent counterproductive outcomes caused by interaction between exercises and unhealthy lifestyle factors. “Inappropriate apoptosis (either too little or too much) is a factor in many human conditions including neurodegenerative diseases, ischemic damage, autoimmune disorders and many types of cancer. The field of apoptosis research has been moving forward at an alarmingly rapid rate”.<sup>[8]</sup> It is possible that both sedentary life and active life could have similar counterproductive or detrimental consequences at the apoptotic level due to malnutrition, sleep issues, alcoholism, smoking, toxicity of

pharmaceutical products, etc., It is also possible for the individuals who exercise regularly associated with avoidance of risky lifestyle factors to develop similar counterproductive consequences at the apoptotic level, exclusively because of inappropriate exercise programs (incorrect exercise intensity, insufficient recovery from exercises). Apoptotic dysfunctions among various individuals at any given point of time could lead to misinterpretation of any prevalent disease in the community as a transmissible disease or an outbreak because there is also a probability that many individuals in the community developing more or less similar illness and clinical features, at the same time. The end products of malfunctioning apoptosis or even normal apoptosis could generate fragmented genetic materials from the dying/dead cells, and some portions of such genetic materials (DNA, RNA) might also be misinterpreted as a causative microorganism. This article aims at critically analyzing apoptosis and lifestyle.

### **Fundamentals of Apoptosis**

“Cell death is probably one of the most widely-studied subjects among cell biologists. Apoptosis is an ordered and orchestrated cellular process that occurs in physiological and pathological conditions. An understanding of the underlying mechanism of apoptosis is important as it plays a pivotal role in the pathogenesis of many diseases. Too much apoptosis and too little apoptosis are the culprits of diseases”.<sup>[9]</sup> “Apoptosis, or programmed cell death, is a crucial mechanism for the survival of organisms and is functionally conserved in all higher eukaryotes. Molecular events in apoptosis are responsible for removal of damaged or infected cells from the cellular population, which links apoptosis to the cell cycle, replication and DNA repair. Moreover, apoptosis is one of the main mechanisms governing accurate embryonic development and maintenance of tissue homeostasis”.<sup>[10]</sup> “We have come to understand apoptosis as

not merely a single form of cell death, but as a fundamental theme in cell biology that has far-reaching implications in the fields of physiology and pathology. In normal tissue, cells that are no longer needed are rapidly eliminated without affecting the overall function of the tissue. In this process cells undergo an active and spontaneous suicide called programmed cell death. In fact, the majority of physiological cell deaths take the form of apoptosis. Cancer cells become resistant to apoptosis, and they become resistant to treatment, metastasize, and proliferate destructively.<sup>[11]</sup> “Apoptosis, or programmed cell death (PCD), is a physiological response that eliminates unwanted cells, an evolutionarily ancient process that is present in all multicellular organisms. Apoptosis is a continually occurring, tightly regulated process that maintains the homeostatic cellular balance in a normal animal. PCD is relatively rarely directly observed in healthy animals. This is because apoptotic cells are potent triggers for phagocytosis and thus are rapidly removed from the environment”.<sup>[12]</sup> “Apoptosis is a morphologically distinct form of cell death which plays a key role in embryogenesis and tissue homeostasis. These are the compaction and marginalisation of chromatin in the nucleus, accompanied by plasma membrane blebbing and cell shrinkage, ultimately forming apoptotic bodies which in vivo are rapidly removed by phagocytosis by neighbouring parenchymal cells or by professional phagocytes. Since the subcellular organelles remain intact and there is little leakage of the contents of the dying cell, apoptosis provides the organism with a safe method of maintaining genome integrity by allowing the organism to remove damaged or abnormal cells without compromising neighbouring cells. This contrasts with necrotic cell death caused by severe cell injury where the cells lyse releasing destructive enzymes and potentially toxic chemicals, which may often cause inflammation. There is no doubt that oxidative stress can elicit cell death, and that

mild oxidative stress can initiate apoptosis rather than necrosis; although reactive oxygen species can cause oxidative stress, they are not essential for the apoptotic processes to occur. A tempting, unifying hypothesis is that perturbation of cellular redox homeostasis may control these key events”.<sup>[13]</sup> Cells also activate apoptosis when they suffer from various insults, such as damage to DNA or to other cellular components, or impairment of basic processes, such as DNA replication and DNA repair.<sup>[14]</sup> “Apoptosis or programmed cell death, is essential for the normal functioning and survival of most multicellular organisms. It is currently believed that apoptosis can be divided into at least three functionally distinct phases, i.e. induction, effector and execution phase. Recent studies have demonstrated that reactive oxygen species (ROS) and the resulting oxidative stress play a pivotal role in apoptosis. Taken together ROS, and the resulting cellular redox change, can be part of signal transduction pathway during apoptosis. It is now established that mitochondria play a prominent role in apoptosis. During mitochondrial dysfunction, several essential players of apoptosis, including pro-caspases, cytochrome C, apoptosis-inducing factor (AIF), and apoptotic protease-activating factor-1 (APAF-1) are released into the cytosol. The multimeric complex formation of cytochrome C, APAF-1 and caspase 9 activates downstream caspases leading to apoptotic cell death. increasing evidences provide support that oxidative stress and apoptosis are closely linked physiological phenomena and are implicated in pathophysiology of some of the chronic diseases including AIDS, autoimmunity, cancer, diabetes mellitus, Alzheimer's and Parkinson's and ischemia of heart and brain”.<sup>[15]</sup> “Living cells maintain genome stability, which is absolutely essential for healthy survival, through complex surveillance and repair systems. Cell cycle arrest, DNA repair and apoptosis may be intercorrelated events aiming at

counteracting a dangerous DNA status. If repair is successful, cell cycle arrest is reversed and cells divide, if not, cells survive with DNA defects or die by apoptosis".<sup>[16]</sup>

### Exercise and Apoptosis

Apoptotic cell death differs morphologically and biochemically from necrotic cell death, although both appear to occur after exercise.<sup>[17]</sup> "Physical exercise is well known to affect leukocyte numbers and function. While regular exercise training has been shown to enhance specific immune functions, acute bouts of intensive exercise often led to a pro-inflammatory response accompanied by a transient lymphocytopenia and neutrophilia. On the other hand, apoptosis might be a regulatory mechanism which is necessary for tissue reorganization and adaptational training processes".<sup>[18]</sup> "Skeletal muscle is unique with respect to apoptotic processes, given its multinucleated morphology and its apoptosis-associated differences related to muscle and (or) fiber type as well as mitochondrial content and (or) subtype. Elevated apoptotic signaling has been reported in skeletal muscle during aging, stress-induced states, and disease; a phenomenon that plays a role in muscle dysfunction, degradation, and atrophy. In general, acute strenuous and eccentric exercise are associated with a proapoptotic phenotype and increased DNA fragmentation (a hallmark of apoptosis), whereas regular exercise training or activity is associated with an antiapoptotic environment and reduced DNA fragmentation in skeletal muscle. Given the current literature, we propose that regular physical activity may represent an effective strategy to decrease apoptotic signaling, and possibly muscle wasting and dysfunction, during aging and disease".<sup>[19]</sup> "Immediately after the exhaustive exercise, the percentage of apoptotic cells increased significantly, whereas it remained unchanged after the moderate exercise. Several reasons suggest that apoptosis is involved in exercise-

induced alterations of the immune system such as postexercise lymphocytopenia".<sup>[20]</sup> "Because lymphocyte apoptosis is significantly elevated immediately following high-intensity exercise in humans, it seems intuitive that the cell death process must be initiated at some point during the task. Exercise intensity threshold for inducing an increase in lymphocyte apoptosis occurs between 40 and 60 % VO<sub>2</sub>max".<sup>[21]</sup> "Neutrophil spontaneous apoptosis, a process crucial for immune regulation, is mainly controlled by alterations in reactive oxygen species (ROS) and mitochondria integrity. Exercise has been proposed to be a physiological way to modulate immunity; while acute severe exercise (ASE) usually impedes immunity, chronic moderate exercise (CME) improves it. It was found while ASE induced an oxidative state and resulted in acceleration of human neutrophil apoptosis, CME delayed neutrophil apoptosis by maintaining a reduced state for long periods of time even after detraining".<sup>[22]</sup>

### DISCUSSION

It is not easy to condense this broad area 'apoptosis' and its extensive interconnections with homeostasis and allostasis in all the phases of human life cycle. "Normal human somatic cells have strictly limited proliferative capacity and reach a state of senescence when it becomes exhausted – *Hayflick Limit*. It is believed that senescence is a response to extensive and irreparable DNA injury, localized in telomeric and/or non-telomeric regions of the genome. Main cause of this damage is oxidative stress, increasing due to deteriorated function of mitochondria. Senescent cells accumulate in tissues during aging, which is causatively linked with the development of various pathologies in elderly individuals".<sup>[23]</sup> "Apoptosis (self-killing) and autophagy (self-eating) constitute the two self-destructive processes by which supernumerary, damaged or aged cells and organelles are eliminated. Beyond this homeostatic function, autophagy is also

a process through which cells adapt their metabolisms to starvation, imposed by decreased extracellular nutrients or by decreased intracellular metabolite concentrations that result from growth-factor signalling. Autophagy constitutes an adaptive response to different kinds of stress by which the cells avoid cell death, in some settings, it can also contribute to the demise of cells. Organellar stress that affects mitochondria and the endoplasmic reticulum can induce a specific autophagic response that leads to the removal of damaged organelles (mitophagy and reticulophagy, respectively) and protects cells. Beyond a threshold (which is lowered when autophagy is inhibited), such stress causes apoptosis<sup>[24]</sup> “In addition to the bona fide autophagy-dependent beneficial effects of exercise, exercise training can contribute in adjusting the level of autophagy in disease states, which may serve to reduce the disease burden. Numerous studies have provided evidence that autophagy is activated in skeletal muscle in response to exercise<sup>[25]</sup> “Emphysema is characterized by enlargement of the distal airspaces in the lungs, and alveolar endothelial and epithelial cell apoptosis induced by cigarette smoke is thought to be a possible mechanism for this cell loss. Our studies show that cell death in response to cigarette smoke was caused by necrosis, and apoptosis may not be responsible for the alveolar walls and inflammation observed in emphysema<sup>[26]</sup> Heavy alcohol consumption over long periods of time can result in severe liver damage, including death of hepatocytes. Apoptosis and necrosis can contribute to hepatocyte death.<sup>[27]</sup> “Chronic high alcohol consumption induces detrimental cardiac effects seems to be initiated by apoptosis leading to a thinning of the ventricular walls. Irreplaceable apoptosis-induced loss of cardiac tissue ultimately leads to heart failure if abstinence is not commenced immediately<sup>[28]</sup> “Aging is characterized by a progressive decline in cardiac function. Aging enhances the susceptibility to

apoptosis in several types of tissues. A critical contributor to the age-related impairment in cardiac function is the loss of cardiac myocytes through “apoptosis”, or programmed cell death<sup>[29]</sup> “The decrease in organ mass with aging (except for the heart) is an important finding. As blood pressure increases with age, the heart has to work harder to maintain its cardiac output, this would predispose to cardiac hypertrophy, an increase in heart mass<sup>[30]</sup> “Metabolic rate of individual organs is lower in older compared with younger individuals. With aging, reductions in the mass of individual organ/tissues and in tissue-specific organ metabolic rate contribute to a reduction in resting metabolic rate (RMR) that in turn promotes changes in body composition favoring increased fat mass and reduced fat-free mass<sup>[31]</sup> “Periods of unloading exacerbate apoptotic signalling in aging muscles. Loss of muscle nuclei leads to atrophy and sarcopenia. When implemented, the appropriate interventions should offset the apoptotic aging-induced net loss of muscle nuclei, reduce and/or slow sarcopenia, and improve muscle function in the elderly<sup>[32]</sup> “Sleep deprivation affects all aspects of health. Adverse health effects by sleep deprivation are still underestimated and undervalued in clinical practice and, to a much greater extent in monitoring human health. Sleep deprivation might induce multiple organ injury with altered cytokines and oxidative stress that may remain undetected. Successive multi-organ injuries scar organs and induce fibrosis, which causes myocardial infarction, diabetes mellitus, and liver and kidney dysfunction. Long-term successive sleep deprivation is linked to chronic diseases in humans<sup>[33]</sup> Level of apoptotic precision will obviously be individual-specific due to lifestyle variations; therefore, medical profession should give immense respect to diversity in fitness excellence and fitness incompetence among humans, and always be cautious about generalizations. Fitness Excellence = Ideal Body Mass x Ability to Counteract

Gravity, but suboptimal exposure of neuromusculoskeletal system to gravitational force leads to Altered Body Composition with Disability (ABCD).<sup>[7]</sup> “Generalization in medical profession should solely depend on invariable facts but due to several reasons, the lack of critical thinking leads to development of faulty evidences or fabricated evidences or unproductive anecdotal evidences. Anything claimed as evidence without objective analysis hardly fits into the standards of science. Evidence becomes ‘fact’ only if it is quantifiable and reproducible (inter-rater and intra-rater reliability) by applying a standardized methodology. Even if the whole scientific community endorses an evidence, one professional could prove everyone or any long-standing practice as incorrect, with right questions and experimental reports”.<sup>[34]</sup> Exercise prescriptions for all the age groups (athletes, non-athletes, patients) need profound knowledge garnered from empirical evidences and literatures to avoid exercise-induced destruction of homeostasis and unpredictable adverse consequences. Exercise planning and execution should be an interdisciplinary procedure (considering various individual-specific determinants of lifestyle and health) although at present this is not strictly adhered and practiced, in general. “Exercise represents a major challenge to whole-body homeostasis provoking widespread perturbations in numerous cells, tissues, and organs that are caused by or are a response to the increased metabolic activity of the contracting skeletal muscles. To meet this challenge, multiple integrated and often redundant responses operate to blunt the homeostatic threats generated by exercise-induced increases in muscle energy and oxygen demand. Molecular techniques led to greater understanding of the multiplicity and complexity of cellular communications done by muscle with other organs (adipose tissue, liver, pancreas, bone, brain) to mediate beneficial effects on health and performance”.<sup>[35]</sup> “With the development of

new drugs, it is common practice for drug manufacturers to measure their pharmacokinetic parameters. This testing involves the discovery of the absorption, distribution, metabolic, excretory and toxicological properties of drugs. The testing is usually done in non-stressful conditions at rest; however, this does not necessarily tell the entire picture as there is increasing knowledge about the effects that high levels of physical activity can have on the pharmacokinetics of some medications. Patients and healthcare providers should be aware that exercise can adversely affect the way some medications are intended to work. Patients taking certain medications should be closely monitored when performing high amounts of physical activity”.<sup>[36]</sup> “Data demonstrates a severe lack of analysis on the possible detrimental action of alcohol in the recovering athlete. However, based on the available experimental evidence in cellular and rodent-models, athletes should remain wary of ingesting alcohol following intense exercise, focusing instead on effective dietary strategies proven to enhance recovery”.<sup>[37]</sup> “Exercise-induced rhabdomyolysis (exRML), a pathophysiological condition of skeletal muscle damage that may cause acute renal failure, liver dysfunction, compartment syndrome, heart failure, arrhythmias, electrolyte imbalance, and in some cases death. People who participate in exercise may not be aware of exRML. Symptoms of exRML are similar to those of delayed onset muscle soreness that can be easily overlooked. Return to the training and exercise through a basic rehabilitation protocol after suffering from exRML”.<sup>[38]</sup> “Clinically, rhabdomyolysis is exhibited by a triad of symptoms: myalgia, weakness, and myoglobinuria, manifested as the classically described tea-colored urine. It is a complex process associated with morbidity and mortality”.<sup>[39]</sup> “It is possible that rhabdomyolysis will be associated with only severe muscular pain without significant weakness and dark urine. The emergency physicians should be vigilant

about that, so that late diagnosis and treatment can lead to acute renal failure and its complication”.<sup>[40]</sup> “Health is determined by several factors including genetic inheritance, personal behaviors, access to quality health care, and the general external environment (such as the quality of air, water, and housing conditions). For some types of social variables, such as socioeconomic status (SES) or poverty, robust evidence of their links to health has existed since the beginning of official record keeping. It should be emphasized at the outset that the social determinants of health can be conceptualized as influencing health at multiple levels throughout the life course (eg., in utero, during infancy and childhood, during pregnancy, or during old age)”.<sup>[41]</sup> More dangerous VIRUS has been shown in Table 1, which is a threat to all the humans and it can affect humans in all the phases of life cycle based on multifactorial causation.

**Table 1: VIRUS** - Vulnerability (addiction, stress, superstition, herd mentality), Iatrogenesis (faulty medical diagnosis and treatment), Rest dysfunctions (Excessive physical activity and inadequate rest, Inadequate physical activity and Excessive rest, sleep disorder, occupational overload), Unbalanced nutrition (malnutrition, undernourishment, dehydration) and Sociocultural abnormalities (malfunctioning political machinery).

<b>V</b>	Vulnerability
<b>I</b>	Iatrogenesis
<b>R</b>	Rest dysfunctions
<b>U</b>	Unbalanced nutrition
<b>S</b>	Sociocultural abnormalities

“Disorders Irreparably Swiftly Epigenetically Attenuate Survival Efficiency (**DISEASE**) for which Nutrition, Oxygen, Rest, Movement, Abode and Love (**NORMAL**) are primarily needed to prevent or overcome diseases. It means any disease can worsen rapidly to become fatal if we ignore the key salutary contributions of Nutrition (adequate energy and hydration), Oxygen (ability of the body to uptake and utilize oxygen), Rest (sleep,

rejuvenation from physical and mental fatigue), Movement (Activities of Daily Living, Exercises), Abode (shelter) and Love (affection of family members, dearest friends and even unknown persons). Public health system must become a noble ‘School of Thought’ (preferably, nation-specific ‘School of Thought’) and eradicate iatrogenesis, pseudoscience, health inequities, statistical malpractices, quackery, professional degradation etc., Important ‘Salutogenic Health Activism’ initiatives incorporating the principles of Salutogenesis, Homeostasis, Lifestyle medicine, Evidence-based practice, Transdisciplinarity and Teamwork, are needed from the immediate future.”<sup>[34]</sup> If infectious diseases should be controlled or eradicated, we should try to proactively curb the infections caused by unhealthy behaviors and iatrogenesis also. “Devastating health problems associated with alcohol use disorder (AUD) include liver cirrhosis, pancreatitis, cardiomyopathies, neuropathies, and dementia. However, the lung also is adversely affected by alcohol abuse, a fact often overlooked by clinicians and the public. Individuals with AUD are more likely to develop pneumonia, tuberculosis, respiratory syncytial virus infection, and acute respiratory distress syndrome”.<sup>[42]</sup> “Cigarettes contain hundreds of different strains of bacteria, including many human pathogens that may play a role in lung diseases and respiratory infections. Bacteria have been known to be present in tobacco leaves, but only a few studies have looked into the contamination, and no research until now has attempted to catalog the bacteria diversity of cigarettes in order to investigate how these bugs may affect smokers or people exposed to second-hand smoke. Some potentially pathogenic organisms found are Acinetobacter, Bacillus, Burkholderia, Clostridium, Klebsiella, Pseudomonas aeruginosa, and Serratia”.<sup>[43]</sup> People with chronic obstructive pulmonary disease and asthma receiving inhaled corticosteroids are at an increased risk of



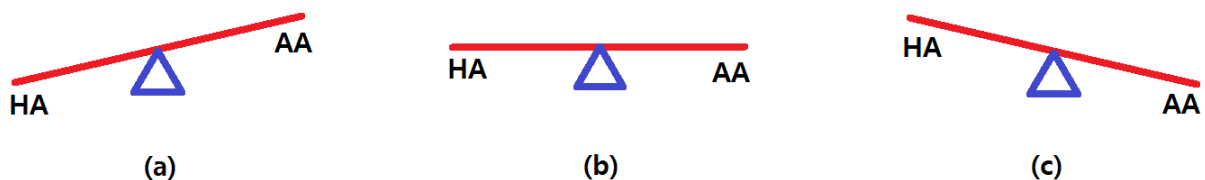
pneumonia or lower respiratory infection, with those receiving higher doses being at greater risk.<sup>[44]</sup> Both rest and exercises render highly beneficial outcomes, only if the individuals control or minimize their allostatic load through self-discipline and cutting-edge scientific approaches to maintain their physiology and homeostatic stability in the Survival Competence Zone (SCZ). Controllable Allostatic Load Zone (CALZ) comes next to the SCZ from which individuals would be able to return to SCZ rapidly through appropriate lifestyle modifications if they are cognizant of their deviation from SCZ, if not, regardless of the age and the phase of life cycle, if the allostatic load increases uncontrollably due to any one of the components or all the components of VIRUS, then the physiology of the individuals would enter into a Transient Maladaptive Zone (TMZ) or Permanent Maladaptive Zone (PMZ). In TMZ or PMZ, both rest and exercises can only render counterproductive or life-threatening outcomes (Table 2 and Figure 1) due to derangements in homeostasis. Therefore, recuperating from TMZ or PMZ becomes a great challenge and misery. Homeostatic apoptosis enables perfect homeostasis (pH) without unnecessary loss of cells and organ mass. Allostatic apoptosis could disturb the homeostatic stability probably leading to diseases almost equally among sedentary individuals and exercisers due to morbidity-exacerbating lifestyle behaviors. “Lifestyle behaviours are

everyday activities that result from individual’s values, knowledge, and norms shaped by broader cultural and socioeconomic context. These behaviours affect overall health and are influenced by a number of social characteristics”.<sup>[45]</sup>

**Table 2:** Homeostatic Apoptosis is possible in SCZ and CALZ through productive lifestyle. Allostatic Apoptosis becomes uncontrollable in TMZ and PMZ due to counterproductive lifestyle. PMZ is characterized by irreversible allostatic load. More cellular deaths, misunderstanding between autophagy and apoptosis, multi-organ dysfunctions, inefficient or totally failed detoxification mechanisms are possible in TMZ and PMZ.



**Figure 1:** Homeostatic Apoptosis (HA) should always dominate and suppress Allostatic Apoptosis (AA) in the body to be in Survival Competence Zone for superior health and healthy aging. If HA and AA are in the equilibrium state, individuals would be probably in CALZ. If AA dominates HA, individuals suffer of morbidities and unhealthy aging, sometimes even irreversible loss of homeostatic functions leading to mortality. In this figure, a = SCZ, b = CALZ, c = TMZ and PMZ.



To refine the medical profession further and maximize its scientific contributions, intellectual humility becomes paramount, and all possible critical thinking and evidences should be invited and organized. “SARS-Cov-2 has never been isolated in

accordance with standard practice. The diversity of symptoms among patients makes it impossible to associate specific symptoms with the presence of SARS-Cov-2 RNA or to isolate the virus with precision. Today, adding impurities from patients to

cell cultures to provoke cytopathic effects is considered sufficient, whereas this does not in any way enable isolation of viral particles or characterization of their genetic material. Significant uncertainty surrounds the isolation of this virus and the characterization of its genome, which are notwithstanding the basis upon which PCR diagnostic tests have been developed. In such circumstances, the point of departure uncertainty has a direct bearing on the general diagnostic reliability".<sup>[46]</sup> If cells undergo too low or too much apoptosis among the individuals in TMZ and PMZ zone especially, the cellular debris in their body may not be efficiently detoxified, thus, the fragmented genetic materials might circulate or deposit in some part of the body and interfere with epigenetics (in addition to defective epigenetics and autophagy) to cause acute and chronic diseases. Such fragmented genetic materials (DNA, RNA) may possess varying genetic codes, because of this, if we develop a diagnostic tool to detect specific genetic code(s) of a microorganism in the human body, a vast majority of the individuals (including those in SCZ, CALZ) would be declared positive for a disease, multiple times in their life, even without any symptoms or illness, all leading to persistent chaos in the human life and society. "*Homo sapiens* is relatively young species and has not had as much time to accumulate genetic variation as have the vast majority of species on earth. Between any two humans, the amount of genetic variation – biochemical individuality – is about 0.1 percent and this means that about one base pair out of every 1000 base pairs will be different between any two individuals. Almost all human genetic variation is relatively insignificant biologically, that is, it has no adaptive significance. Notwithstanding the genetic differences between individuals, all humans have a great deal of their genetic information in common. Analysis of human genetic variation also confirms that humans share much of their genetic information with the rest of the natural world – an indication

of the relatedness of all life by descent with modification from common ancestors".<sup>[47]</sup> If the universal goal is to ensure only homeostatic apoptosis to function in the human body (ie.,SCZ) in the all the phases of the human life cycle, the medical profession as a whole along with the political machinery should shift its orientation towards salutogenesis. "Antonovsky distinctly stated that salutogenesis was not limited by the disciplinary borders of one profession but rather an interdisciplinary approach and a question of bringing coherence between disciplines and realise what connects them through the people's ability to comprehend the whole situation and the capacity to use the resources available (called as sense of coherence - SOC) to move in a health promoting direction".<sup>[48]</sup>

## CONCLUSION

Though the data is limited, the empirical evidences show recurrent illness history among the individuals who undergo structured exercises associated with significant improvements (associated with or without favorable changes in body weight and body composition) as compared to their baseline exercise tolerance standards. Such phenomena may exist because, simultaneously, different variants of rhabdomyolysis or multi-organ dysfunctions are affecting the exercisers who fail to support their exercises with a disciplined lifestyle but many such illnesses may go unnoticed or often get misdiagnosed. Another important prominent feature is the inability of the exercisers to rapidly return to their peak personal exercise standards after acquiring, and recovering from, such illnesses. Due to incorporation of unhealthy lifestyle factors, both sedentary individuals and exercising individuals could experience almost similar morbidities in their lifespan, due to mild to severe apoptotic errors. Both health and disease operate on a multifactorial background, thus applied knowledge in assessments like Rothman's Causal Pie Model becomes crucial.

Especially, individuals should not set risky unrealistic goals to lose body weight at a rapid pace by hook or crook because such weight loss pursuits may be accompanied by miscalculated apoptosis and multi-organ dysfunctions ultimately causing unnecessary loss of cells and organ mass although the intended outcome is loss of unwanted 'fat mass' only. In view of the aggravating uncertainties created by asymptomatic and symptomatic transmission of infections, an immunological classification system (preferably based on 'Exercise Tolerance Diversity' and 'Somatotype Diversity') should be discovered as it becomes necessary to quantitatively measure the immunologic strengths of humans in all the phases of life cycle. It is extremely difficult to promote health if either the exercisers are unknown about the possible counterproductive interactions of exercises and risky lifestyle behaviors or if they simply assume that exercises are great antidote for those risky lifestyle behaviors, so there is no need to abandon those unhealthy behaviors. But meticulous homeostatic apoptosis can only be expected if exercises are supported by appropriate healthy lifestyle. In contrary, erroneous allostatic apoptosis is inevitable if exercises are unsupported by appropriate healthy lifestyle, thus individuals would suffer illnesses (sometimes recurrent illnesses) despite exercise participation which means the prophylactic and therapeutic effects of exercises may not happen at all in the body but counterproductive outcomes may happen. Strengthening of the non-pharmacological salutogenic approaches need thorough understanding of Benchmark Homeostatic Traits (BHT) of the individuals who engage in laborious physical activity at their occupation or sports training amidst highly challenging environmental conditions. Humans should perceive their life as enjoyable and productive in all the phases of their life cycle, but, at some stages in the life cycle they would be in a state of bewilderment and equally perceive their life and death as fearful and distressful due to

worsening or recurrence of diseases caused by heavy allostatic load, and after certain level of irreversible loss of homeostasis and survival competence, they would perceive life as meaningless and death as meaningful to permanently get rid of their excruciating ailments. At the cellular level, the enjoyability and productivity of human life depends on durable homeostatic stability regulated by faultless apoptosis.

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