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Physical Exercises: From the Evolutionary Thriftiness to the Epigenetics of Contemporary Diseases and Current Therapeutics for Physical Inactivity Diseasomes

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ABSTRACT

For millions of years, our ancestors had been faced with survival stresses including famine, thirst, infection, trauma and physical stress and, for approximately 84,000 generation, survived as hunter- gatherers, in the wild required daily expenditure energy for requisite activities as foraging and/or hunting for food and water, social interaction, confrontation with or flight from predators, making and maintaining shelters and clothing, and other. To cope with the injury responses, a coordination of neuroendocrine, energy storage, water economy and immune systems are adapted and developed a thrifty genotype that permitted our ancestors to continue intense physical activities, despite prolonged fasted states. With the switch to a sedentary lifestyle and sodium- and energy-rich diets, the thrifty genotype was no longer advantageous, and may be maladaptive to disease phenotype. Physical inactivity leads to accumulation of ectopic fat and consequently the activation of a network of inflammatory pathways, which promote metabolic disturbances as well as a network of chronic diseases, belonging to the 'diseasome' of physical inactivity. Ancient physicians believed in the value of physical activity for health, called "exercise factor" and, current evidence suggests that the protective effect may be ascribed mostly to its

anti-inflammatory effects. The over the century sought exercise-induced "humoral factors" that mediated cross-talk between contracting muscles and other organs now it is known as myokines. By releasing myokines, physical exercise modulates the function of many physiological systems and, many of the exercise-induced changes are attributed to epigenetic chromatin remodeling. Physical activity could therefore be a natural remedy for recovering part of the imbalance caused by modern life-styles, costless and without the side effects of many pharmacological treatments. In this context, physical exercises have profound implications for public health and have been used as a preventive and/or complementary therapeutic strategy for our lifestyle-change protocols.

Key words: Physical Exercise Thriftiness; Physical Inactivity and Modern Diseases; Diseasome of Physical Inactivity; Chromatin Remodeling by Exercise Training; Therapeutic Exercises

ABBREVIATIONS: Angiotensin-Converting Enzyme **(ACE)**; Attention Deficit Hyperactivity Disorder **(ADHD);** Protein Kinase B **(Akt);** Adenosine Monophosphate **(AMP);** Adenosine Monophosphate-Activated Protein Kinase **(AMPK)**; Apoptosis-Associated Speck-Like Protein Containing a Caspase Recruitment Domain **(ASC);** Angiotensin ii Type 1 Receptor **(AT1R);** Before Christ **(BC);** Brain-Derived Neurotrophic Factor **(BDNF);** Body Mass Index **(BMI);** Ca^{2+}/Calmodulin-Dependent Protein Kinase **(CaMK);** Creb-Binding Protein **(CBP);** cAMP Response Element Binding Protein **(CREB);** Cardio Respiratory Fitness **(CRF);** Cardiovascular Diseases**(CVDs);** Deoxyribonucleic Acid **(DNA)**; Endothelial No Synthase **(eNOS);** Free Fatty Acids **(FFAs);** Glucose Transporter Type 4 **(GLUT4)**; Glucocorticoid Receptors **(GRs);** Hour **(H)**; Histone Acetyltransferase **(HATs);** Histone Deacetylases **(HDAC);** Heat Shock Protein **(HSP)**; Impaired Plasma Glucose **(IFG)**; Interleukin **(IL);** Interleukin 1 Receptor Antagonist **(IL-1Ra);** Kilocalories **(Kcal);** kilograms **(Kg);** Pound **(lb);** Low Density Lipoprotein **(LDL);** Lifestyle Modification **(LiSM);** Monocyte Chemo attractant Protein-1(**(MCP-1);** Myocyte-Specific Enhancer Fator **(MEF);** Metabolic Syndrome **(MetS);** Myosin Heavy Chain Genes **(MHCs);** Matrix Metalloproteinases **(MMPs);** Month **(mo);** Myogenic Differentiation 1**(MyoD1);** Non Esterified Fatty Acids (**NEFA);** Nuclear Factor k B **(NF- κB);** Nlr Family Pyrin Domain Containing 3 **(NLRP);** Nitric Oxide **(NO);** Nuclear Respiratory Factor 1**(NRF-1);** Pyruvate Dehydrogenase Kinase 4 **(PDK4);** Peroxisome proliferator-activated receptor-γ co activator **(PGC-1alpha)**; Phosphoinositide 3-Kinase **(PI3K);** Peroxisome Proliferator-Activated Receptor Gamma **(PPAR-γ);** Peroxisome Proliferator-Activated Receptor Delta **(PPAR-δ);** Randomized Controlled Trials **(RCT);** Ribonucleic Acid **(RNA);** Sirtuin **(Sirt);** Type 2 Diabetes Mellitus **(T2DM);** Mitochondrial Transcription Factor 1**(TFAM);** Toll Like Receptor **(TLR);** Tumor Necrosis Factor Alpha **(TNF-α);** Tropomyosin Receptor Kinase B **(TrkB);** Vascular Cell Adhesion Molecular-1**(VCAM-1);** Vascular Endothelial Growth Factor **(VEGF);** World Health Organization **(WHO);** Week **(wk);** Year **(yr)**

THE NATURAL SELECTION SURVIVAL IN ADVERSE ENVIRONMENT

Evolution by natural selection is a central organizing concept in biology once natural selection shapes organisms in functioning within a particular set of environmental conditions [1].

For millions of years, living creatures from lower-level organisms to human beings have been faced with stresses. Our ancestors were often faced with survival stresses, including famine, infection, trauma and physical stress [2].

To cope with the injury responses, a coordination of neuroendocrine, energy storage, water economy and immune systems are adapted. It is known that an activation of the innate and adaptive immune system demands high energy consumption.

The Thrifty Genotype

Since regulation of energy storage and metabolism and the preservation of body fluids are critical for organism's fight against famine, infection and physical stress, the survival pressures drove our evolution to shape a thrifty genotype, which favored/promoted energy-saving and sodium/water preservation [3].

Humans represent a thrifty species relative to some other mammals. Thrifty implies some degree of prosperity deriving from earlier frugality and a careful management of resources. This indicates that metabolic adaptations had a crucial role in the emergence of present day Homo Sapien lineage, in particular in buffering reproduction from ecological stochasticity [4].

A thrifty genotype was initially defined as "being exceptionally efficient in the intake and/or utilization of food" [5].

The thrifty gene hypothesis suggests we evolved genes for efficient food collection and energy-yielding deposit to survive periods of famine. This would lead to the thrifty phenotype hypothesis [6], which postulates that under conditions of suboptimal in utero nutrition, the fetus must adapt to its environment to ensure survival of the organism, through a "sparing" of vital organs such as the brain at the expense of organs such as pancreas, kidney and skeletal muscle. Thrifty phenotype represents a short-term adaptive response (preserving vital organs at the expense of less essential traits) to poor energy availability [7].

For doing it so, it was proposed that metabolic programming occurs to promote nutrient storage to provide a survival advantage in conditions of poor post-natal nutrition [6].

The Thrifty Phenotype

The history of human populations since the late Paleolithic era has been characterized by a fight for survival in the face of food shortage, epidemics and changes in climate encountered during migrations [8].

Oscillations of muscle glycogen and triglyceride levels with physical activity-rest cycles during feast-famine over tens of thousands of years selected some genotypes and genes to oscillate, some of which might also play a role in efficiency during fuel usage. During a famine state, regulatory biochemical processes, with insulin resistance, may develop in order to conserve and avoid a loss of skeletal muscle glycogen and fatty acid in starvation [9].

Inflammatory cytokines released from activated immune cells inhibits insulin signaling pathway; as a result, plasma levels of glucose are elevated to provide energy sources to maintain the function of vital organs (heart, brain and immune cells) and combat for the infection [10,11].

In addition to its metabolic effects, insulin induces vaso-relaxation and regulates sodium homeostasis by enhancing sodium re absorption in the kidney, thereby, contributing to the regulation of blood pressure. Therefore, negative regulation of insulin signaling could be viewed as a physiologic 'adaptive mechanism" that is activated in certain conditions such as fasting, inflammation, stress and pregnancy [12].

The Thriftiness of Physical Activity

The famine-induced insulin resistance may be reversed by exercise in order to conserve muscle glycogen stores by oxidizing greater quantities of fatty acids. This 'thrifty' regulation allows skeletal muscle to consume enough energy and permitted our ancestors to continue intense physical activities to hunt for food, despite prolonged fasted states [9].

It is probable that evolution selected these genes for glucose storage and conservation in order to rapidly provide the energy necessary for immediate tasks related to muscle work and survival. The fact that both feast-famine and exercise-rest cycles produce oscillations in glycogen concentration implies that some of the glycogen cycling regulatory mechanisms for the above two hunter-gatherer situations could be common [13].

Studies in experimental models manipulating muscle glycogen content with exercise have revealed several possible candidates as "thrifty" genes. Among the genes that efficiently conserve the utilization of muscle glycogen were pyruvate dehydrogenase kinase-4, hexokinase, IL-6 and HSP72 [14-16].

The increased glucose uptake by muscle can be obtained insulin-independently through activation in muscle cells of a cascade of molecular signals, promoting the gene expression of GLUT4 [17].

Similarly, independently of fed state, prolonged endurance exercise elicits a variety of metabolic and morphological gene expression including those related to mitochondrial biogenesis, fast slow fiber-type transformation and substrate metabolism. In contrast, heavy resistance exercise stimulates synthesis of contractile proteins responsible for muscle hypertrophy and maximal contractile force output [18].

In general, exercise promotes several beneficial cardiovascular effects mainly by reducing or preventing oxidative stress and inflammation. The vasodilatation and anti-oxidant effects are mainly by increasing NO bioavailability [19,20].

The control of the release and activity of at least two cytokines ("tumor necrosis factor-α" TNF-α and IL-6) may contribute to the natural protective effect of physical activity.

During exercise, contracting skeletal muscles release anti-inflammatory myokines (IL-6, IL-10 and IL-1Ra). IL-6 inhibits TNF-α production in adipose tissue and macrophages [21].

THE PHYSICAL ACTIVITY TRANSITION

Our ancestors, for approximately 84,000 generation, survived as hunter- gatherers. To survive in the wild required large expenditure energy on a daily basis for requisite activities such as foraging and/or hunting for food and water, social interaction, confrontation with or flight from predators, making and maintaining shelters and clothing, and other. A physically active existence predominated throughout most of human history, leading up to and continuing 45,000 yr after the emergence of the modern human genome (i.e., *Homo sapiens sapiens*) [22].

More evidence for this statement comes from recorded activity levels of remaining contemporary hunter- gatherer/agrarian societies. The Machiguenga Indians, in Peru, both men and women work at physically demanding tasks (i.e., hunting, farming, traveling by foot) an average of 8.5-9.5 h/day. A study with these Indians revealed an average energy expenditure of 60 kcal.kg $^{-1}$ .day $^{-1}$ for Machiguenga men compared with a value of 39 kcal.kg $^{-1}$. Day $^{-1}$ for US men [23]. This represents a staggering 35% decrease in individual energy turnover potentially resulting from industrialization of society (~1,600 kcal/day or 167 lb. of body fat/yr for a 75-kg individual)! The energy expenditure of hunter-gatherers during physical activity (~1,000-1,500 kcal/day) can be reached with 3-4 h/day of moderate-to-vigorous physical activity, e.g., brisk/very brisk walking [24,25].

People's levels of physical activity have changed dramatically as a result of the move from pheasant-agricultural to urban-industrial ways of life. Technological improvements over just ~350 generations (agricultural followed by industrial and, most recently, digital revolution) have led to dramatic reductions in human physical activity levels. For though, economic development has the effect of reducing levels of occupational household and transport physical activity. Changes in degrees of physical activity throughout the world have been rapid since 1970s as household work has become increasingly mechanized and vehicles are used more often for transport. Thus, the overall reason for dropping physical activity is due to lower physical expenditure in occupational, household and transport which have become increasingly mechanized. Recreational activity is the only area in which physical activity may increase although people may not necessarily use their leisure time for active pursuits. However, there are other factors constraining physical activity in cities such as personal safety and town planning.

At the beginning of this century WHO [26] estimated that at least 60% of the world's population fails to achieve the minimum recommended of 30 min/day of physical activity [27,28]. More recently it was estimated that ~ 1/3 of adults worldwide were inactive, and the endemic inactivity trend starts in early life [29].

The Epigenomics of Physical Activity

The history of human populations since the late Palaeolithic era has been characterized by a fight for survival in the face of food shortage, epidemics and changes in climate encountered during migrations [8].

A hunter-gatherer (nomadic) and perhaps equally active agrarian society dominated during that time, only changing recently with the beginning of the industrial revolution, a little more than 100 yr ago. Hence, a physically active existence predominated throughout most of human history, leading up to and continuing 45,000 yr after the emergence of the modern human genome (i.e., *Homo sapiens sapiens*) [22].

Our ancestors therefore lived and evolved in a much more physically demanding environment than is seen in current industrialized societies. Humanity's gene pool was selected when man's remote ancestors lived as Stone Age hunter-gatherers. Certainly, today's prevalently sedentary lifestyle directly contradicts one of the natural forces driving the evolution of our genes. There have been few subsequent genetic changes despite the agricultural and industrial innovations of recent millennia [30].

In comparison with the millennial pace of genetic evolution, human technological and social evolution has occurred at light speed. This incongruence has left us genetically adapted for the demands of life as a forager in the wild despite the fact that we are living in a high-tech, sedentary, overfed, emotionally-stressed 21st century world [31].

The profound and progressively wider discrepancy between current day physical activity and the indigenous Homo sapiens exercise patterns predictably results in atrophy, disability and disease. Nowadays it is known that physical exercise modulates the function of many physiological systems, such as the musculoskeletal, the cardiovascular and the nervous system, by inducing various adaptations to the increased mechanical load and/or metabolic stress of exercise. Genes require the stimulus of physical activity to promote a state of health. Many of these changes occur through epigenetic alterations of DNA, such as his tone modifications, DNA methylations, expression of microRNAs and changes of the chromatin structure [32].

The Mismatch of Ancestral Genome with the Modern Lifestyle

Our ancestors (primitive humans) had to undertake considerable physical activity to gain food and had to adapt to prolonged period of famine, which favored fat storage, a trail inherited by modern man [33].

In our modern lifestyle, characterized by energy-rich Western diet, sedentary life and high psychosocial stress, favors positive energy balance. In the long term, this positive energy balance creates the need for surplus fat storage [34].

In humans, obesity may be considered as a symptom of energy imbalance: caloric intake exceeds energy expenditure. When the capacity for safe lipid storage in adipose tissue is exceeded lipids overflow to non-adipose tissue, increasing the risk for chronic systemic low grade inflammation [2,35].

Similarly, the accumulation of sodium in tissue has been presumed to be accompanied by a commensurate retention of water to maintain the isotonicity of body fluids [12,36].

Consequently, sodium-conserving (thrifty) genotype may be maladaptive to the modern environment of sodium abundance, resulting in hypertension [3]. Thus, with the switch to a sedentary, the thrifty genotype is no longer advantageous, and may be maladaptive to disease phenotype, resulting in hypertension, obesity and insulin resistance syndrome. Insulin resistance and hypertension are considered to be Western diseases. Natural selection of thrifty genotype, which was a physiological adaptive mechanism for human survival, on the current obesogenic environment, is maladaptive to disease phenotype [12].

Our modern lifestyle, characterized by energy- and sodium-rich Western diet, sedentary life and high psychosocial stress, favors positive energy balance. In the long term, this positive energy balance creates the need for surplus fat storage [34] Meals high in saturated fat, as well as meals high in calories have been associated with increases in inflammatory markers [37,38]. When the capacity for safe lipid storage in adipose tissue is exceeded lipids overflow to non-adipose tissue, increasing the risk for chronic systemic low grade inflammation and subsequent insulin resistance, hypertension and metabolic syndrome [35]. It has become clear that most, if not all, typically Western chronic diseases find their primary causes in unhealthy lifestyles and that systemic low grade inflammation is a common denominator [2,33,34].

Lifestyle factors and human health are linked through epigenetics mechanisms. Epigenetics can be defined as somatically heritable states of gene expression resulting from changes in chromatic structure without alterations with DNA sequence. Because epigenetic modifications can be altered by external or internal environmental factors and have the ability to change gene expression, epigenetics is now considered an important mechanism in the unknown etiology of many diseases. Epigenetics is highlighted in fields such as inflammation, obesity, insulin resistance, type 2 diabetes mellitus, cardiovascular diseases, neurodegenerative diseases and immune diseases.

EPIDEMIOLOGY OF PHYSICAL INACTIVITY

It was shown that chronic diseases such as coronary heart disease, hypertension, diabetes, and some forms of cancer are also virtually unknown in contemporary hunter-gatherer societies, even in those individuals over 60 yr of age. These findings indicate that the increased prevalence of chronic diseases in industrialized societies may be an inactivity-related phenomenon and also argue against those who would claim that chronic diseases are on the rise solely because people are now living longer [22].

Physical inactivity is a major, if not the primary, cause of the increased prevalence of chronic diseases in our modern, largely sedentary society [39].

Epidemiological data have established that physical inactivity increases the incidence of at least 17 unhealthy conditions, almost all of which are chronic diseases or considered risk factors for chronic diseases. A strong association existed between the increase in physical inactivity and the emergence of modern chronic diseases in 20th century industrialized societies. Approximately 250,000 deaths per year in the United States are premature due to physical inactivity States [40,41].

Physical inactivity increases the risk of type 2 diabetes [42], cardiovascular disease [43], colon cancer [44], postmenopausal breast cancer [45], dementia [46] and depression [47]. These are all frequent chronic diseases, associated with an enhanced risk of premature morbidity. Clearly, independently of body mass index **(BMI)**, physical inactivity is a risk factor for all-cause mortality [48]. On average, physically inactive people have a life span that is 5 years shorter than that of physically active people. Moreover, the expected lifetime without long-standing illness is reduced by approximately 8 years in physically inactive people [49]. Hence, lack of adequate physical activity is linked to type 2 diabetes, obesity, cardiovascular diseases, certain cancers, neuro-degeneration, muscle skeletal disorders and other pathologies, thereby increasing morbidity and mortality and reducing the quality of life as well as overall life expectancy [50]. Thus, physical inactivity might be considered the biggest public health problem of the 21st century [51]. Decrease in or removal this unhealthy behavior could improve health substantially worldwide [52].

THE DISEASOMA OF PHYSICAL INACTIVITY

Researchers in the area suggested that physical inactivity leads to accumulation of visceral and ectopic fat (fat accumulated in non-adipose tissue cells) and consequently the activation of a network of inflammatory pathways, which promote the development of insulin resistance, atherosclerosis, neuro degeneration, tumor growth, as well as a network of chronic diseases, including cardiovascular diseases **(CVDs)**, type 2 diabetes, Alzheimer disease and other disorders belonging to the 'diseasome' of physical inactivity [48]. Hence, visceral fat and chronic inflammation accompanied the diseases within the "diseasome of physical inactivity", potentially explaining the clustering of these chronic disorders in epidemiological studies [53]. The diseasome of physical inactivity represents diseases with highly different phenotypical presentations, but that share important pathogenetic mechanisms. Thus, it has been suggested that type 2 diabetes, CVD, colon cancer, breast cancer, dementia and depression constitute a cluster of diseases, which defines a diseasome of physical inactivity [48].

THE CONCEPT OF "EXERCISE FACTOR" FOR HEALTH PROMOTION

Ancient physicians, including Chinese (2600 BC) and Hippocrates (400 BC) believed in the value of physical activity for health. In the past, the role of physical activity as a life-style

modulating factor has been considered as that of a tool to balance energy intake. However, evidence suggests that the protective effect of exercise may to some extent be ascribed to the anti-inflammatory effect of regular exercise. Exercise may exert its anti-inflammatory effect via a reduction in visceral fat mass and/or by induction of an anti-inflammatory environment with each bout of exercise [53].

The early view on the "exercise factor" concept was predicated by the fact that contracting skeletal muscle mediates metabolic and physiologic responses in other organs that are not mediated via the nervous system [54]. The idea was supported by findings from electrical stimulation of paralyzed muscles in spinal cord-injured patients. It was obvious that one or more muscle-derived humoral factors existed and, for lack of more exact knowledge, these humoral factors were called the 'work stimulus' or the 'work factor' [55]. The plural form 'exercise factors' would be more applicable, given the fact that multiple metabolic and physiologic changes are induced by exercise. Contracting skeletal muscles must, therefore, be able to communicate to other organs via humoral factors, which are released into the circulation during physical activity. Such factors might directly or indirectly influence the function of other organs such as adipose tissue, liver, the cardiovascular system and the brain [53]. In this context, the identification of muscle as a cytokine-producing organ was a breakthrough. The idea that muscle cells might produce and release a humoral factor dates back many years before the identification of adipose tissue as an endocrine organ. For nearly half a century, researchers had hypothesized that skeletal muscle cells possess a 'humoral' factor that is released in response to increased glucose demand during contraction [56]. In the year 2000, it became clear that contracting human skeletal muscle releases significant amounts of interleukin **(IL)**-6, firstly named myokine, into the circulation during prolonged single-limb exercise [57]. Myokines provide a conceptual basis to explain how muscles communicate to other organs [53].

Presently, it is known that skeletal-muscle fibers can produce several hundred secreted factors, including proteins, growth factors, cytokines, and metallopeptidases [58-62], with such secretory capacity increasing during muscle contractions [63-69], myogenesis [60,70,71], and muscle remodeling [72], or after exercise training [62]. Muscle-derived molecules exerting either paracrine or endocrine effects [66] are strong candidates to make up a substantial fraction of the exercise polyp ill excerpting putative protective role against disease phenotypes.

Pleiotropic Positive Effects of Physical Exercise

It is well known that exercise satisfies essential requirements for a healthy life. There is strong epidemiological evidence indicating that regular physical activity is associated with reduced rates of all-cause mortality, CVD, hypertension, stroke, metabolic syndrome, type 2 diabetes, breast and colon cancer, depression, and falling [52]. Athletes, who are those humans sustaining the highest possible physical activity levels, live longer than their nonathletic counterparts [73]. Physical exercise is a unique physiological stressor that is capable of inducing adaptations in nearly all

cells, tissues and organs [74]. Small changes induced by exercise can create a ripple effect of benefits to the entire body while, exercise probably has pleiotropic positive effects in almost every organ system [53]. In fact, exercise and, especially the contracting muscle is indeed a source of numerous drug-like molecules with beneficial effects across all ages. Definitely, exercise, even in the absence of significant weight loss, is an excellent preventative and therapeutic intervention for many chronic disorders [75]. One of the most prominent effects of exercise is the improvement in physical capacity of both healthy individuals and those with a disease [74]. But, there is strong epidemiological evidence on the beneficial effects of regular exercise, which are likely to go well beyond reducing CVD risk factors. Furthermore, exercise benefits can overcome those of common drugs when one considers that the exercise polyp ill combines preventive, multi-systemic effects with little adverse consequences and at lower cost [76].

MOLECULAR AND EPIGENETIC BASIS OF HEALTHY EXERCISE

Regular exercise is probably the lifestyle intervention with the most profound up regulating effect on hundreds of genes involved in tissue maintenance and homeostasis [76].

Physical exercise causes alterations in the expression of human skeletal muscle genes, as a mechanism of adaptation not only to the mechanical load but also to the metabolic stress of exercise. Many of those changes in gene expression can occur through epigenetic regulations which are induced by exercise and are related to metabolic processes [77-79].

The most common epigenetic changes induced by exercise are his tone modifications, such as methylation and acetylation, DNA methylation, and expression of different types of microRNAs **(miRNAs)** [80].

In general, acute exercise causes hypomethylation of the whole genome in the skeletal muscle cells of sedentary people. This hypomethylation is mainly related to promoters of metabolic genes (e.g., PGC-1alpha, TFAM, PPAR-δ, PDK4, citrate synthase) and results in increased gene expression. However, the transcription of muscle-specific transcription factors, such as MyoD1 and myocyte-specific enhancer factor **(MEF)** 2A, does not change [81].

Exercise can also lead to changes in the action of cytosolic messengers such as Ca^{2+} and AMP, which result in the activation of signaling cascades and eventually to alterations in gene transcription. These alterations occur through the activation of Ca^{2+}/Calmodulin-dependent protein kinase **(CaMK)** and AMP-dependent protein kinase **(AMPK)** [82].

Aerobic exercise has been shown to cause mainly a reduction in the expression of various types of miRNAs in human skeletal muscle, 22% of which target genes that regulate transcription and 16% target genes that are involved in muscle metabolism, especially in oxidative phosphorylation.

The decrease in miRNAs expression causes an increase in the expression of mitochondrial and lipid oxidation enzymes, without affecting the amount of the mRNA of metabolic genes [83].

GLUT4 Expression

AMPK can change the expression of genes, such as the glucose transporter type 4 **(GLUT4)** by activating cellular transcription factors and co- activators in mammalian skeletal muscle. Following acute exercise, AMPK phosphorylates HDAC5, causing its dissociation from MEF2. This dissociation enables MEF2 to interact with co-activators such as PPAR-γ, PGC1alpha and HATs, acetylating GLUT4 and, thus, increasing its expression [84,85].

Specifically for the mitochondrial genes, it has been suggested that AMPK activates the PGC-1α co-activator, which increases the expression of other transcription factors that, in turn, lead to the transcriptional changes [86].

Also HDACs can regulate the expression of PGC-1α, which is increased after exercise in an intensity-dependent manner, and is a key factor in the human muscle adaptation to exercise [87,88].

Over-expression of PGC-1α and nuclear respiratory factor 1 **(NRF-1)** appears to increase the expression of the GLUT4 and the activity of MEF2 implying that AMPK could increase the expression of GLUT4 protein through PGC-1α pathway [89-91].

Such exercise-induced genetic modifications could have clinical implications. Specifically, in type 2 diabetic patients, PPAR-γ and PGC-1α are hypermethylated in human skeletal muscle. This hypermethylation has been correlated with reduced mRNA expression of PGC-1α and mitochondrial DNA [92].

Thus, exercise may have a beneficial effect on the prevention and confrontation of type 2 diabetes and other metabolic disorders through the afore-mentioned epigenetic mechanisms, since it can increase not only the expression of GLUT4 in muscle, but also the hypomethylation of PPAR-γ and PGC-1α [93,94].

Transcription of Myosin Heavy-Chain Genes

Epigenetic alterations due to physical activity status can regulate the transcription of myosin heavy chain genes **(MHCs)** [95].

In particular, acetylation and methylation of histone H3 at specific states is related to a differential expression of I MHC, IIx MHC and IIb MHC genes in soleus muscle following reduced muscular activity (muscle de loading) [96,97].

In addition, HDAC5 has been found to increase the number of type I oxidative fibers following exercise [98].

Anti-Inflammatory Actions

The anti-inflammatory effects of regular exercise may be mediated via both a reduction in visceral fat mass (with a subsequent decreased release of adipokines) and the induction of an anti-inflammatory environment with each bout of exercise [99].

Chronic exercise training can decrease the circulating levels of toll like receptor **(TLR)** ligands, specifically, saturated free fatty acids **(FFAs)** and oxidized low density lipoproteins **(LDLs)** that are known to be elevated in metabolic disease [100]. FFA leads to inflammasome activation and IL-1β release through an AMPK-autophagy-ROS signaling pathway. When activated, such as by physical exercise, the adenosine monophosphate-activated protein kinase **(AMPK)**, an essential mediator of fatty acid metabolism [101], results in an increased β oxidation of FFAs in mitochondria and decreased overall lipid load inside cells [102]. Furthermore, it is important to note that elevated levels of NEFAs associated with insulin resistance, obesity, Type 2 diabetes and the metabolic syndrome activate innate immune inflammatory pathways upstream of nuclear factor κ B (**NF- κB**), a key transcription factor that is involved in the regulation of many of the pro-inflammatory genes, including TNF-α (tumour necrosis factor-α), IL (interleukin)-6, MCP-1 (monocyte chemoattractant protein-1) and adhesion molecules [e.g. VCAM-1 (vascular cell adhesion molecular-1)] [103].

By decreasing intracellular FFA and metabolites the reactive oxygen species **(ROS)** generation is decreased. However, there are several features of acute exercise and chronic exercise training that suggest that a principal anti- inflammatory effect of exercise may be mediated via effects on TLR pathway activation. Specifically, exercise may reduce the availability of endogenous TLR4 ligands, decrease the expression of TLR4, and decrease the activation of TLR4 signaling [99,104].

Apoptosis-associated speck-like protein containing a caspase recruitment domain **(ASC)** is a mediator of the cytosol-type inflammatory signaling pathway [105,106].

Physical exercise decreases the expression of ASC gene and, in turn, the activation of inflammatory cytokines. In fact, it has been shown that chronic moderate exercise up-regulates the methylation status of ASC, resulting in a decreased activity of the gene in human monocytic cells and, thus, preventing the activation of inflammatory cytokines, such as IL and TNF [107,108].

Epigenetic alterations can also regulate the binding of transcriptional factor NFκB to DNA, which is indispensable for various pro-inflammatory cytokines to be expressed [109].

The HDACs reinforce the NFκB -DNA binding, while HATs impair it [110].

Overall, the exercise reduces activation of both TLR4 and the NLRP3 inflammasome and, therefore, reduce the levels of IL-1beta as well as the NF-κB. All these epigenetic modifications ensure the proper functions at the cellular level, because the inflammatory responses are balanced by the expression of anti-inflammatory genes, in physical exercises [111].

Preservation of Vascular-Endothelium Functions

Physical exercise exerts a great impact on cardiovascular system [112].

Exercise promotes several beneficial cardiovascular effects mainly by reducing or preventing oxidative stress and inflammation through at least two distinct pathways. Via mechano-receptor

stimulation, high shear stress up-regulates and stimulates proteins in the Akt/eNOS pathway and NO production. Concomitantly, physical exercise down-regulates endothelial AT1R (angiotensin II type 1 receptor) expression and, may inhibit p47 translocation, leading to a decrease in NADPH oxidase activity and superoxide anion production, which in turn decreases ROS (reactive oxygen species) generation, and preserves endothelial NO bioavailability [113].

During the exercise-induced cardiac hypertrophy, new sarcomeres are added both in parallel and in series, increasing the length of the cardiac cells. This results in an increased ventricular stroke volume and cardiac output, which improves aerobic capacity. Hence, exercise training causes a non-pathological increase of the myocardial mass, resulting in cardiac hypertrophy and neo-angiogenesis-"the athlete's heart" [114].

However, deregulation of HAT/HDAC ratio, or of their function, can also lead to modified expression of matrix metalloproteinases **(MMPs)**, which are related to pathological alterations of vascular walls, to altered proliferation of endothelium myocytes in heart and vessels, and even to lethal cardiomyopathy [115-117].

Regular physical exercise can have a protective role against cardiovascular diseases, by restoring HAT and HDAC activity to the normal condition, and by regulating these epigenetic mechanisms [113].

In addition, it has been shown that aerobic exercise training modulates numerous miRNAs, which in turn regulate their target mRNAs and, thus, provoke the physiological cardiac hypertrophy, through different signaling pathways [114].

Aerobic exercise causes an increase in the levels of miRNA-29a, -29b and -29c, resulting in decreased expression of collagens I and III **(COLIAI and COLIIIAI)**, an increase in the expression of miRNA-27a and -27b, resulting in decreased levels of angiotensin-converting enzyme 1 **(ACE1)**, and a decrease in the levels of miRNA-143, which increases the expression of angiotensin-converting enzyme 2 **(ACE2)** [115,116].

All these effects promote the growth and differentiation of cardiac cells, the ventricle compliance, the anti-fibrosis and, eventually, the physiological cardiac hypertrophy [117].

Cardiac hypertrophy includes neo-angiogenesis as well and, aerobic exercise promotes the cardiac angiogenesis through the VEGF pathway and its targets that converge in an increase in the angiogenic pathways MAPK and PI3K/Akt/eNOS [118].

It should be noted that the signaling pathways that lead to cardiac hypertrophy and are induced by exercise protect the heart from fibrosis and pathological remodeling, and they are different from those that provoke pathological hypertrophy and may present a different expression pattern of miRNAs [114,117].

Taking into consideration that cardiac hypertrophy is a major problem in many cardiac diseases, either the enhancement of miRNAs via miRNA-mimics, or the silencing of miRNAs, via miRNA-antagonists, could be regarded as a hopeful approach that may help the onset of new therapeutic strategies against cardiac diseases [119,120].

Carcinogenesis Prevention and Progression

Physical activity is currently suggested as a protective factor against cancer, which lowers the risk of cancer occurrence and mortality [121,122].

Exercise may prevent the progression of carcinogenesis and improve cancer survival through its influence on the epigenetic regulation of either tumor suppressor genes or the inflammatory processes [32].

An underlying mechanism for carcinogenesis is chronic inflammation that can be mediated by ASC protein [107].

As it has been aforementioned, physical exercise decreases the expression of ASC gene through epigenetic mechanisms, and, in turn, the activation of inflammatory cytokines. Thus, exercise can protect the cell from an inflammatory environment which could promote carcinogenesis [32].

in general, physical activity is usually associated with higher levels of global genomic DNA methylation and, thus, it could restore, at least to some extent, the hypomethylated genome in cancer [123].

Not only global hypomethylation but also promoter hypermethylation has been associated with neoplasmatic mutations in the genome. Actually, in most types of human neoplasms, a methylation of cytosine in CpG dinucleotides in gene promoters appears to be associated with transcriptional gene silencing [124,125].

An aberrant DNA methylation may result in silencing of a tumor-suppressor gene, which is a crucial component of the mechanism of carcinogenesis such as in the case of gastric and breast cancer and other tumors as well as the suppressor protein p53, which is down-regulated in many types of cancer, through epigenetic mechanisms including miRNAs [126-129]. Physical exercise may diminishes or reverses promoter hypermethylation of tumor suppressor genes allowing their expression. Furthermore, physical exercise decreases estrogen levels, which have been proposed as inducers of promoter hypermethylation of tumor suppressor genes and are implicated in breast cancer carcinogenesis [129,130].

Preservation of Brain Plasticity and Cognition

Various studies have revealed evidences that strongly indicate an important role of exercise on brain plasticity and cognition. Those effects of exercise are mainly mediated through the actions of brain-derived neurotrophic factor **(BDNF)**, a neurotrophin which is highly expressed in hippocampus and contributes to neuronal development [131].

BDNF can act as a mediator between metabolism and brain plasticity, because it is regulated by protein molecules, such as AMPK, which is up regulated by physical exercise [132].

Exercise has a beneficial effect on remodeling the chromatin region which contains BDNF gene, making it accessible to the indispensable transcriptional factors and, thus, inducing the expression of BDNF. Acetylation of histone H3 along with a reduction of HDAC5 levels result in the transcription of BDNF gene, indicating that H3 is an important molecule which mediates epigenetic regulations following exercise [133-135]. This hyperacetylation status has been found to be associated with enhanced transcriptional activity [136-138].

The impact of exercise on BDNF is mediated by the calcium/calmodulin-dependent protein kinase II **(CaMKII)** signaling system and by the transcription regulator cAMP response element binding protein **(CREB)** [139,140]. In particular, it has been shown that BDNF is associated not only with the effect of exercise on hippocampal synaptic plasticity, but also is involved in neuronal excitability, and particularly in the functions of learning and memory [141-148].

Hence, these described exercise-induced effects are likely to contribute to the promotion of mental health and resistance to neurological disorders and brain syndromes, since many of them, such as Alzheimer, depression, manic episodes, bipolar disorder, REM sleep deprivation, and attention deficit hyperactivity disorder **(ADHD)** are caused by the lack of BDNF [142,149-152].

More specifically, it has been shown that physical exercise alleviates the symptoms of ADHD. Indeed, regardless of its type (i.e., endurance or resistance exercise), can partially restore the decreased levels of BDNF, improving both the neurobehavioral deficits and the biomarkers associated with ADHD [153].

With regard to the REM sleep deprivation, Zagaar et al. [154] found that regular exercise prevents impairments in short-term memory caused by sleep deprivation. They stressed that exercise-induced compensatory mechanisms, regulated by epigenetic modifications, prevent down-regulating changes in the basal and post-stimulation levels of P-CaMKII and BDNF, which are associated with sleep deprivation.

Exercise enhances epigenetic mechanisms and gene expression in hippocampus, improving cognitive response to psychological stress [141].

This occurs through increased phosphoacetylation of histone H3 and higher c-Fos responses, which are caused by exercise. Additionally, by increasing the expression of glucocorticoid receptors **(GRs)**, exercise enhances the effect of stress-induced elevations of glucocorticoid hormone levels in rodents [155,156].

Another area, where physical exercise has positive effects by up-regulating the BDNF levels, is neurogenesis [157]. Indeed, the survival and the integration of the newborn neurons in adult brain rely on the good functioning of BDNF/TrkB signaling [158]. In this context, the positive impact of exercise on neurogenesis may be beneficial against various neurodegenerative disorders, such

as Alzheimer's disease. In fact, there is evidence supporting that a loss of neuronal acetylation is associated with neurodegeneration, since under neurodegenerative conditions there is a decrease of histone acetylation levels as seen with the loss of CBP-HAT activity [159]. In this regard, exercise increases synaptic integrity and neuroplasticity in the brain, and simultaneously improves memory, learning and stress responses [160].

In fact, apart from up-regulating BDNF, exercise can also alter the activity of hippocampus by changing the HAT/HDAC ratio. Exercise reduces HDAC activity and increases HAT activity in the hippocampus, thus increasing the HAT/HDAC ratio [161]. In that context, exercise, which induces histone acetylation and restores HAT/HDAC balance, has been regarded as an important strategy in neuroprotection and memory function, in order to prevent or accelerate recovery in neurodegenerative diseases [162-164]. Thus, physical exercise causes epigenetic modifications, which regulate the transcriptional mechanisms of several genes in the brain, coordinating the adaptive behavioral responses to stressful events [32].

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Modulation of Aging Processes

Aging is a natural process that is usually associated with numerous pathologies and homeostatic deregulations. Aging is usually associated with great shortening of telomeres that can lead to cellular damage [165].

There are studies in humans, suggesting that physical exercise is an inducer of telomerase activity and gene transcription, coding for proteins that stabilize telomeres, through epigenetic mechanisms [166].

Another family of molecules related to aging is sirtuins **(Sirts)** [167]. Studies indicate that physical exercise has different effects on Sirt1 activity, depending on the type of exercise and on the part of the animal or human body where the Sirt1 activity was measured [168].

It is supposed that physical exercise regulates, probably through epigenetic mechanisms, the Sirt1 activity which, in turn, regulates important signaling molecules, such as PGC- 1alpha, p53, NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and other transcriptional factors. All these molecules play a key role in cellular energy metabolism, gene transcription and, consequently, in cell survival [32].

PHYSICAL EXERCISE AS TOOL IN LIFESTYLE CHANGE INITIATIVES

There are plenty of statistics to support the contention that there has been an epidemic emergence of modern chronic diseases in the latter part of the 20th century and, continue on

this century. It is estimated that these costs are now approaching $1 trillion and stand to further dramatically increase as the baby boom generation ages. Because this approach has been largely unsuccessful in reversing the epidemic, it is argued that more emphasis must be placed on novel approaches such as *primary prevention*, which requires attacking the environmental roots of these conditions. Preventing a chronic disease in the first place is more humane and produces less suffering than treatment/secondary prevention of overt disease. It is also much less expensive to society in terms of health care costs [169].

Physical activity could therefore be a natural remedy for recovering part of the imbalance caused by modern life-styles in bodies "born to run" and fed parsimoniously [13].

A Community-Based Experience

Move for Health (*Mexa-se Pró-saúde*) is an on- going epidemiological study conducted by professionals from the Nutritional and Exercise Metabolism Centre (CeMENutri) of the UNESP Medical School (Botucatu, SP, Brazil). The program introduces healthy lifestyle modification **(LiSM)** into subject's diary activities by promoting nutritional re-education and supervised physical exercise as primary care for chronic non-communicable diseases. Patients are submitted to assessments of clinical, anthropometric, dietary, physical activity, blood analysis, fitness (aerobic, strength and flexibility), and postural at baseline and after 10 wk interventions (daily sessions of supervised exercises and dietary counseling). The program exists since 1991 free of charge in the first 10wk and is permanently open for registration. Different protocols of exercises and dietary interventions were conducted in free-living adults to verify the effects of lifestyle changes (diet and physical fitness) on obesity, diabetes, hypertension, dyslipidemia, and metabolic syndrome [170-174].

Lifestyle changing program, including supervised physical exercises (cross-training 65% to 85% HR, 80min, ≥ 3 times/wk) and dietary counseling (monthly) resulted, after two years, in body (6.1%) and abdominal (2%) fatness normalization [175]. Six months of this protocol was effective to reduce 60.5% of overweight subjects with impaired fasting glucose in a RCT [176]. Additionally, by applying the protocol to hypertensive non-medicated men the normalization of blood pressure achieved 46.5% after 8 months [172].

A 24.2% reduction of MetS was found when subjects were submitted to supervise cross training and dietary counseling protocol during 6 months. However, 10.8% of non-MetS subjects at baseline developed MetS at the end of intervention [177]. Furthermore, a reduction of MetS from 47% to 40% was reached with 60 subjects (53yrs, 84% women) after attending a 20wks of lifestyle change program composed by a weekly nutritional counseling and physical activities combining aerobic (3 times/wk) and resistance (2 times/wk) exercises [178].

The 10-week high dietary fiber intake intervention combined with cross-training exercises was associated with a 24% reduction of MetS incidence while it increased 6% in the control-exercised group [179].

Three grams a day of PUFA (360 mg of docosahexaenoic acid and 540 mg of eicosapentaenoic acid) associated with cross-training exercises and with dietary counseling protocol were investigated in a RCT using LiSM. After 20 weeks of intervention both groups increased CRF and the reduction of MetS found in the W-3 PUFA intervention group was 29%, mainly due to normalization of blood pressure (33%) and triglycerides (27.3%), and the decreasing of waist circumference [180].

Considering the estimated extra cost of overweight/obese Brazilians as being US$0.50/ subject (US$36 mi/72573.235 subjects) the economy of this LiSM for the public health (3.4% eutrophy promotion) would be of US$ 1.23 mi in either 6 months of LiSM with exercises and dietary counseling or in 2 months of LiSM associated with dietary fiber intervention [181].

The efficacy of the LiSM by reducing existing T2DM (>126 mg/dL) was 50% and, it was 60.5% in reducing impaired fasting glucose (IFG ≥ 100 mg/dL) after a 6mo. Intervention [176]. After 20-week intervention, normoglicemics, IFG and T2DM responded similarly to LiSM and both genders increased body fatness. Overall T2DM decreased 68% from M0 (9.5%) to M1 (6.4%) of LiSM [182].

The 60% effectiveness rate of our LiSM would affect 11.25 million (15.4%) of Brazilians receiving oral hypoglycemic agents from the public health system. Given the US$ 3.9 billion annual cost of diabetes and from that 5% as the oral agent costs, if applied nationwide this LiSM would save US$ 195 mi/yr or, by using the 6.76% rate (oral agent/ hospitalization expenditures) the Brazilian Public save would amount US$ 16.49 million a year! [176].

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