Allostasis, Homeostasis, and Fluidomechanic Effect of Exercise in Maintaining Health Condition

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Abstract: Noncommunicable diseases (NCDs) are responsible for more than 68-75% of deaths. Leading risk factors for premature death include physically inactivity, obesity, hypertension and smoking. Health related physical fitness (Hr-Pf) is the way to prevent these comorbidities, consist of cardiorespiratory endurance, body composition, muscular strength, muscular endurance and flexibility. The principle of maintaining Hr-Pf are maintaining homeostasis state, stabilizing the body system during changes, strengthening body system to bear the allostatic load and achieving the better homeostasis state. This article will discuss about how the body response to the changes of homestasis, allostatic state and allostatic load during life and the role of fluidomechanic adaptation during exercise affects the allostatic state in cellular to tissue level.

1 INTRODUCTION

Noncommunicable diseases (NCDs), such as diabetes, cardiovascular diseases, cancer, chronic respiratory diseases, and mental disorders are responsible for more than 68% of deaths worldwide and 75% of deaths in low- and middle-income countries. Leading risk factors for premature death include physical inactivity, obesity, hypertension, and smoking. Physical fitness from exercise can prevent the reduced cardiorespiratory fitness, which represents a global public health problem, that in turn leads to morbidity, disability and mortality of some diseases. Health-related physical fitness (Hr-Pf) components consists of cardiorespi-ratory endurance, body composition, muscular strength, muscular endurance and joint flexibility.

The principle of maintaining Hr-Pf are maintaining homeostasis state, stabilizing the body system during changes, strengthening body system to bear the allostatic load and achieving the better homeostasis state. Homeostasis is an ability of the body to seek and maintain a condition of equilibrium or stability within its internal environment when dealing with external changes, a dynamic process continuously. This process clamps each internal parameter at a "set point" by sensing errors and correcting them with negative feedback (Berntson and Cacioppo, 2007).

2 DISCUSSION

2.1 Homeostasis: Adjustment to Failure.

Homeostasis refers to the processes by which the constancy of the fluid matrix is maintained. During maintaining the equilibrium, there are conditions ranged from adjustments (health state) to failures (illness/injured state), which can occur progressively (Figure 1). Homeostasis processes may continue to operate at the basic regulatory level, being sensitive to internal physiological stimuli that signal deviations from a regulated set point. Exogenous stimuli may reset regulatory levels, either directly or via a humoral route, to facilitate resistance or adaptation to the exogenous stressor. Such readjustments of set-point deviate from homeostatic or hemodynamic processes, as they represent active alterations of the regulatory level, named Heterostasis. Heterostatic regulation could be affected by the changes of hormones and the

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chemical environment of the body (Bertnson and Cacioppo, 2007).

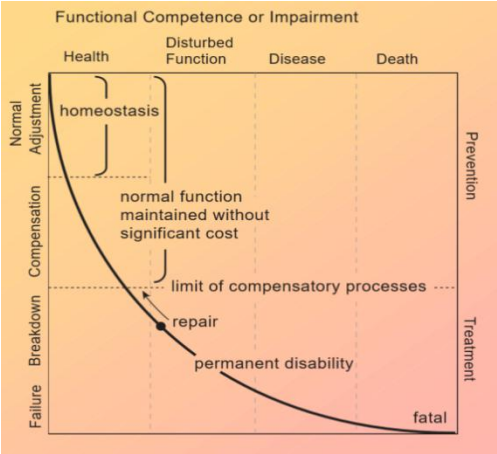

Figure 1: Adjustment to failure (Berntson and Cacioppo, 2007)

2.2 Allostasis : Stability Through Change.

Regulatory levels are not fixed, but may be flexibly adjusted to meet changing demands. The uncompensated condition is occurred when the stressors overcome ability of the body to compensate the changes. This condition is called allostasis. Allostasis is a wide range of functioning of the coping/adaptation systems, depending on a variety of factors. Many visceral dimensions are regulated by multiple interacting mechanisms that are subject to a wide range of modulatory influences, that reflecting the natural adaptive readjustment of regulatory levels in changing physiological demands. It reflects the operations of higher neural systems that control and integrate a broad range of more basic "homeostatic" reflexes (Berntson and Cacioppo, 2007).

Sympathetic-Adrenal-Medullary (SAM) axis (which release catecholamines) and Hypothalamus-Pitutary-Adrenal (HPA) axis (which produce glucocorticoids) are regulatory systems involved in allostasis (Bertson and Cacioppo, 2007).The goal of this process is not constancy, but rather fitness under natural selection, with strategies of preventing errors and minimizing costs, using prior information to predict demand and then adjusting all parameters to meet it. This process is triggered by allostasis load/stress, which has consequences of cost (coping or adaptation), wear and tear on the brain and body, and if the ongoing stress continues, the stress responses never turn off and lead to illness and disease.

2.3 Allostatic Load

Generalized model of stress response, shifted the focus from the autonomic nervous system to the pituitary adrenocortical system, termed the General Adaptation Syndrome (GAS) (2). General adaptation syndrome is the sum of all non-specific, systemic reactions of the body which ensue upon long continued exposure to stress, giving the predictable pattern of physical response. It consists of alarm reaction, resistance stage and stage of exhaustion. Alarm reaction is an initial shock response from autonomic nervous system activation within first 6-48 hours after stress (reduced activity). After few days (48 hours – 1 months after stress) of prolonged stress, the organism entering the resistance stage (adrenocorticosteroid response), seems to adapt to the stress and return to normal. In the stage of exhaustion, the acquired adaptation to the stress is lost because of depletion of defensive resources within 1-3 months after stress (Bertnson and Cacioppo, 2007).

Allostatic load can be measured by parameters : 1) Systolic and diastolic blood pressure (indices of cardiovascular activity); 2) Waist-hip ratio (an index of more chronic levels of metabolism and adipose tissue deposition, thought to be influenced by increased glucocorticoid activity); 3) Serum HDL and Total Cholesterol (related to the development of atherosclerosis – increased risks being seen with higher levels in the case of total cholesterol and lower levels in the case of HDL; 4) Glycosylated hemoglobin plasma (an integrated measure of glucose metabolism over several day times); 5) Dihydroepiandrosterone sulfate (DHEA-S) serum (a functional HPA axis antagonist); 6) Overnight urinary cortisol excretion (an integrated measure of 12-hr HPA axis activity); 7) Overnight urinary noradrenalin and adrenalin excretion (integrated indices of 12-hr sympathetic nervous systems activity)

Allostasis causes the allostatic states within tissues and cells, giving load (allostatic load) that affect physical and mental health (Figure 2). Allostatic states reflect tissue and cell's response to allostatic changes (Pederson, 2019 see Table 1

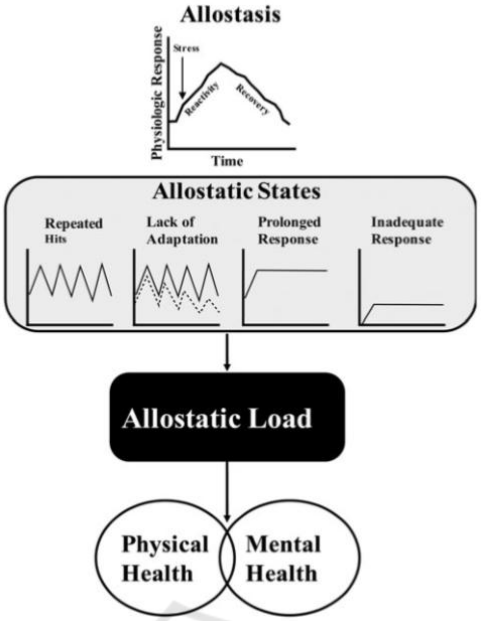

Figure 2: Allostasis, allostatic states and allostatic load (Juster et al, 2016)

Table 1: How the body function response to the stress

Functions Stimulated by Stress	Functions Inhibited by Stress
• Cardiovascular – ↑Cardiac rate – ↑Blood pressure – ↑Blood coagulation – Redistribution of blood from peripheral (skin) and internal systems (GI) to heart, skeletal muscle, brain • Respiratory – ↑Respiratory ventilation • Metabolic – ↑Glycogen mobilization – ↑ Glycemia – ↑Lipolysis • Hormonal – ↑CRH, ACTH, Glucocorticoids – ↑Vasopressin, NGF – ↑Cathecolamines (E & NE)	All functions not immediately necessary for defense and survival are decreased : • ↓Growth • ↓Appetite (anorexia) • ↓Reproductive function & sex drive • ↓Circulation in tissues not involved in stress response • ↓Response to pain • ↓Immune Function • ↓Thymus size • ↓Thymic hormones & cytokines

2.4 Mitochondrial Allostatic Load (MAL)

Chronic stress perturbs adaptive glucocorticoid signaling and glucose levels that in turn alter mitochondrial structure and function, generating oxidative stress and cellular damage. This process cumulatively worsens risk factors, which consequently leads to disease. In this multilevel cascade, mitochondrial dysfunction is depicted as an early event mediating the relationship between primary mediators of chronic stress and disease trajectories (Figure 3) (Juster, 2016).

Mitochondrial allostatic load (MAL) leads to mitochondrial dysfunction, with the manifestations of decreased energy production, increased oxidative stress, pro-apoptotic signaling, mitochondrial DNA copy number alteration, mitochondrial fragmentation, pro-inflammation signaling and transcriptional changes. Physical activity and healthy diet inhibit the allostatic load become MAL, but poor sleep and physical inactivity leads MAL trigger the

dysfunction of specific tissue/organ, that in turn leads to comorbidity that can be seen as clinical phenotype (Juster, 2016).

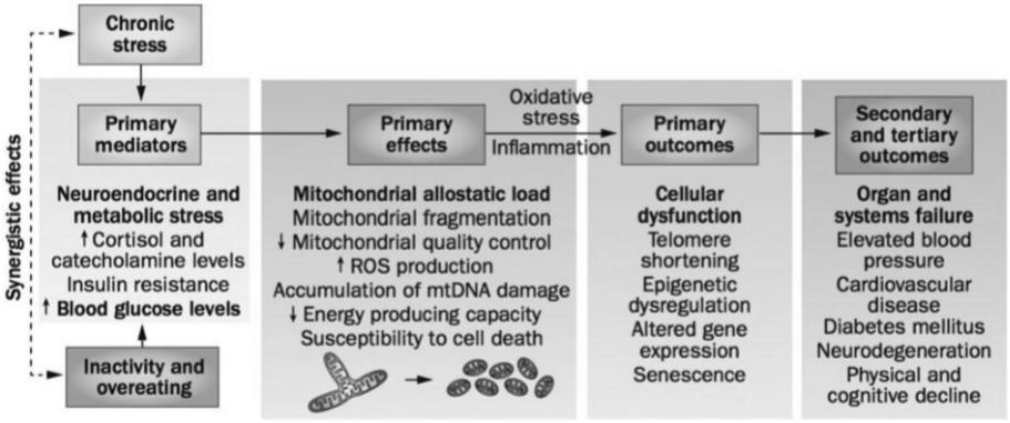

Figure 3: The stress-disease cascade and mitochondrial alloastatic load (Juster, 2016)

2.5 Physiological Toughness Model

Shorter duration of the stress response could reduce the allostatic load and overall wear and tear on the body. Evidence suggests that fitness or exercise training may provide a more rapid recovery from the stressor once it is no longer present. Exercise can reduce the immediate effects of stress and enhance the recovery process from stressors. Intermittent but regular exposure to stressors (e.g., regular exercise) lead to psychological coping, emotional stability, and physiological changes, giving adaptive performance in challenge/threat situations, enhancement of immune system function, and greater stress tolerance. Physical activity and exercise give the benefits such as lowering the risk of death from any cause and in improving longevity, comparable to drug intervention (Pedersen, 2019).

2.6 Exercise and Blood Flow

Popliteal artery was impaired after 5 days of reduced daily physical activity (from >10,000 steps/day to <5,000 steps/day), because decrease in blood flow and thus shear stress, which is an important stimulus for maintaining endothelial health. This impairment can be abrogated by increasing leg vascular shear stress with leg muscle contraction (Teixeira et al, 2017). Muscle contraction during exercise increases the muscular blood flow from muscle pump effect, vasodilator mechanisms and blunting of sympathetic vasoconstriction in contracting muscles (Joyner and Casey, 2015). Muscle blood flow is closely matched to the metabolic demands of contraction, which occurs across a range of intensities from rest to heavy exercise and during both small and large muscle mass exercise, in response to both single contractions and more prolonged exercise lasting for hours (Joyner and Casey, 2017). In human subject, exercise training for 4 weeks increase blood flow capacity (BFC) as measured by reactive hyperemic responses to occlusion of blood flow on limbs. The increase of BFC depends on mode of training and interaction of muscle fiber-type composition with muscle fiber recruitment pattern during exercise. Sprint training has been shown to increase contractile activity in fast-twitch, white skeletal muscle. In contrast, endurance training has been shown increase in contractile activity slow-twitch, red skeletal muscle. Both modes increase oxidative capacity, capillary density and BFC, but sprint mode also triggers changes in vascular cells (Laughilin and Roseguini, 2008).

Increased oxygen demand in exercise is reflected as VO2max, an important factor that increases the blood flow. The variability of VO2max is affected by body composition, level of physical activity, blood volume, hemoglobin mass, stroke volume and "genetic" factors (Joyner and Casey, 2015). Treadmill exercise is one of exercise mimicking natural walking activity, recruits the small and large muscle mass to contract. As the type of exercise, Treadmill exercise should have the specific dose, which the goal is improving the overall fitness which is reflected by VO2max. Uda'a et al reported that in untrained healthy young males, VO2max increased 17% (p=0.000) after 4 weeks of moderate-intensity Treadmill exercises with the modes of

graded increase in speed and graded increase in inclination, and no significant differences between these two modes (Uda'a et al, 2019), but they showed the different heart rate response due to the different modes (graded increase in inclination vs speed) of moderate intensity Treadmill exercise (Figure 4) (Hendrarati,et.al,2019).

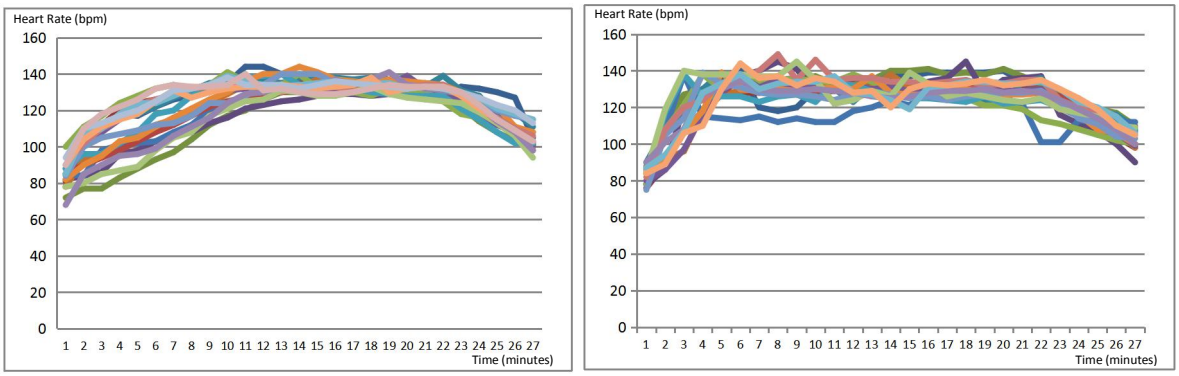

Figure 4: Heart rate response of untrained healthy young males exercise with moderate intensity (70% maximal heart rate) graded increased inclination Treadmill exercise (A) and graded increase speed Treadmill exercise (B) for 30 minutes (Hendrarati et al, 2019).

The peak of target heart rate is achieved earlier in the mode of graded increase in speed (start on minute 3) than graded increase in inclination (start on minute 11) ($p=0.006$). The duration in maintaining the target heart rate longer in increased speed mode (19 minutes) compared to increased inclination mode (11 minutes) ($p=0.000$) (Hendrarati et al, 2019). Longer duration to maintain the muscle exercise, more oxygen and metabolism demand occur, more increase in mitochondrial activity and cellular expression.

Increased blood flow will increase shear force on tissue to cell (Figure 5). Force is transferred across multiple length scales (left) while tissues adapt to the dynamic mechanical environment (right). Together, the transfer of force from the environment, and subsequent structure-function adaptation of the system constitute the dynamic process of functional adaptation, also referred to as mechanoadaptation (Ng JL et al, 2017).

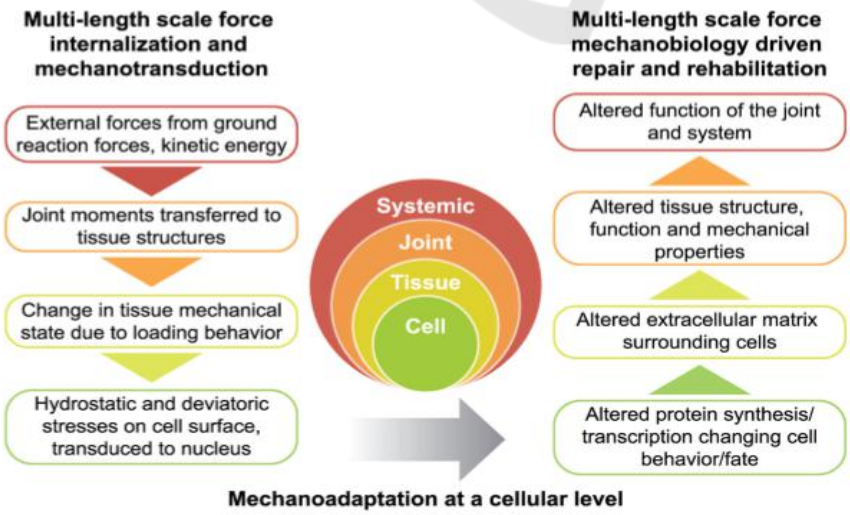

Figure 5: Adaptation to force in tissue to cell (Ng JL et al, 2017).

Blood cellular mechanoadaptation affect the hemorheology. Human blood is a non-Newtonian fluid, so viscosity is not constant at different flow rates. Whole blood viscosity (WBV) is dependent on the shear rate and changes in a non-linear relationship (WBV decreases with higher shear rate) and the temperature (WBV decreases with high temperatures). The principal determinants of WBV are hematocrit, red blood cell (RBC) deformability and plasma viscosity (Cowan et al, 2012). Hematocrit and plasma viscosity rose with exercise, while erythrocyte elongation index is lowered. Acute response of submaximal aerobic exercise (70% HRmax) for 1 hour does not change the blood viscosity, erythrocyte aggregation and fibrinogen, in both young people and adults (Romagnolia et al, 2014). But regular (chronic) exercise decrease hematrocrit (I^2=96.46%), red blood cell aggregation (I^2=94.95%) & plasma viscosity (I^2=99.25%) (Figure 6)(Romain et al, 2011).

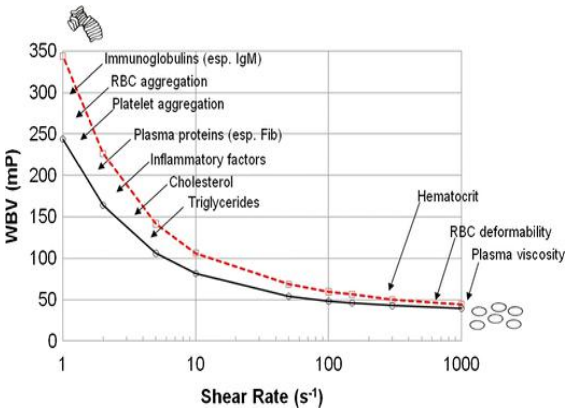

Figure 6: Shear rate and Whole Blood Viscosity.

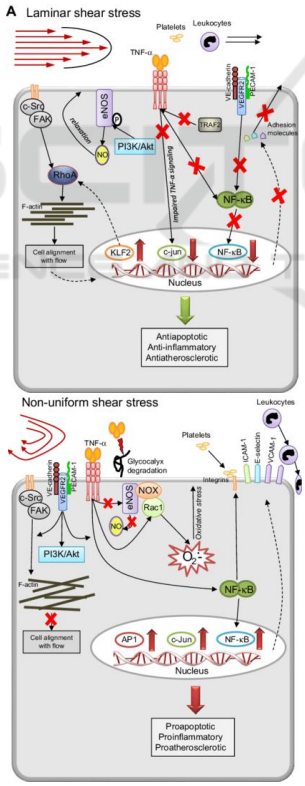

Figure 7. Physical activity and endothelial function (1Kim B et al, 2014)

Shear force/stress is needed for functioning vascular endothelial. Increased in intensity and duration of shear stress from increased blood flow, will increase endothelial Nitric Oxide Species (eNOS) expression and in turn affect the longevity (anti-apoptotic, anti-inflammatory) and function of endothel (vasodilatation, anticoagulation, antiadhesion, fibrinolysis). This mechanism is showed in Figure 7 (Thosar et al, 2012).

2.7 Exercise and Cellular Mechanical Forces.

Mechanical forces (MF) working in cell consist of external and internal MF. External MF is defined as forces, such as tensile, compressive or shear stresses that are applied to cells from their environment, specifically. Internal MF referred to intercellular tension, which can be done by cross bridging of actomyosin, focal adhesion (cell traction forces/CTFs) and substrate stiffness (Wang and Li, 2010).

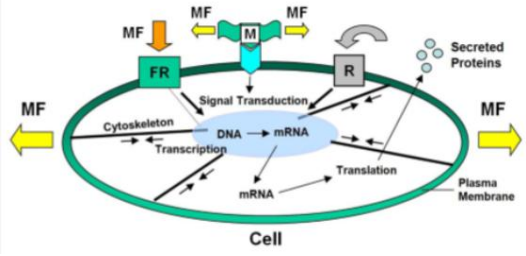

Figure 8: Schematic illustration of the mechanical nature of cellular mechanotransduction mechanism (Wang and Li, 2010).

MF can induce mechanotransduction by directly altering conformation of an extracellular matrix (ECM) protein and integrin configuration and

transmitting forces to the cytoskeleton and nucleus, then eventually affecting transcription and translation. MF can unfold a domain of the extracellular protein (M) and expose a cryptic site that may serve an activating ligand for a cell surface receptor, resulting in a series of signaling events. When MF is applied to force receptor (FR), such as integrin and G protein, they initiate signal transduction, lead to transcription followed by translation. As a result, soluble factors are secreted into the ECM, which act on the receptor (R) and then initiate a cascade of signaling events (Wang and Li, 2010).

In vivo cells integrate and interact with a microenvironment comprised of a milieu of biochemical, biomechanical, and bioelectrical signals derived from surrounding cells, ECM and soluble factors. These components vary in both time and space and are integral to the regulation of cellular behaviors. The biological, chemical, and mechanical properties of biomaterials can also be tuned to further control the cellular microenvironment (Selimovi et al, 2013).

2.8 Exercise and Extracellular Matrix

In contracting skeletal muscle, lower levels of extracellular matrix (ECM) crosslinking reduce the stiffness of skeletal muscle, resulting in improved mechanical properties and mechanotransduction to the resident stem cells. Resistance training (RT) reduces fat infiltration in aging skeletal muscle and is an effective strategy to maintain skeletal muscle mass and cross-sectional area with age. RT blunted the age-induced accumulation of connective tissue concomitant to the up regulation of genes related to the synthesis (COL-1A1/COL-3A1; TGFβ and CTGF) and degradation (MMP-2/MMP-9; TIMP-1/TIMP-2) of the ECM network. Exercise training can potently stimulate stem cell activation and positively influence skeletal muscle ECM remodeling in a manner that suggests both factors are important and perhaps codependent in their ability to improve and/or maintain muscle structure and function following a physiological stimulus (Uda'a et al, 2019).

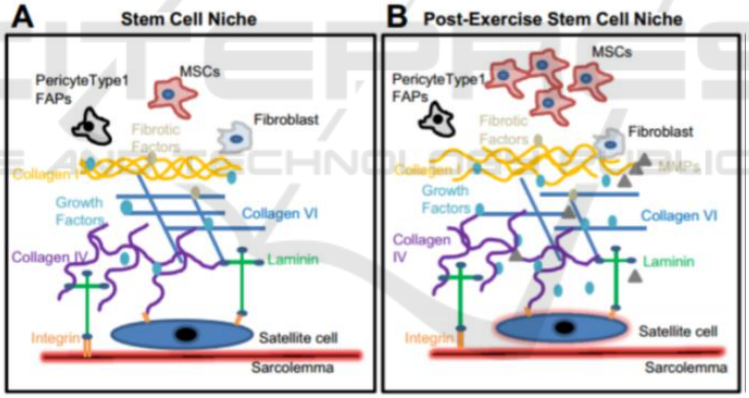

Figure 9: Schematic representation of the skeletal muscle stem cell niche (A) and its alteration postexercise (B). Exercise results in increased mesenchymal stem cell (MSC) accumulation and ECM reorganization facilitated by matrix metalloproteinases (MMPs) (Modified with permission from Taylor & Francis Ltd. (http://www.tandfonline.com) (Garg and Boppart, 2016)

2.9 Exercise and Endocrine Effects

Activated muscle contraction during exercise, act as endocrine organ and communicate with other organs. Brain-derived neurotropic factor (BDNF) and Interleukin (IL)-6 are involved in 5'-AMP-activated protein kinase (AMPK)-mediated fat oxidation. IL-6 stimulates lipolysis, involved in glucose and lipid metabolism and stimulates cortisol production (only during exercise), neutrocytosis and lymphopenia. Irisin is involved in the "browning" of white adipose tissue (Pedersen, 2019). In untrained young healthy males, Irisin serum significantly increase acutely after 1 session of moderate intensity Treadmill exercise with graded increase in speed mode ($p=0.002$), but not in graded increase in inclination mode. The baseline Irisin serum increased 5% after 2 weeks exercise (Uda'a et al, 2019). In the same subjects, baseline BDNF serum increased significantly (111%) after 2 weeks of moderate intensity Treadmill exercise with graded increase in

speed mode (p=0.001), but not in graded increase in inclination mode. There was no significant acute response in BDNF after exercise (Yulinta et al, 2019). This facts showed that each myokine have specific response in term of mode of exercise and its role on the specific target organ.

The muscle secretome consists of several hundred secreted peptides, as communicator with other organ. IL-4, IL-6, IL-7, IL-15 and LIF (Leukemia Inhibitory Factor) promote muscle hypertrophy. Myostatin inhibits muscle hypertrophy and exercise leads to liver secretion of the myostatin inhibitor follistatin. IL-6 also increases insulin secretion by inducing the expression of Glucagon Like Peptide (GLP)-1 by the L cells of the intestine. IL-6 has anti-inflammatory effects because it inhibits TNF production and stimulates the production of IL-1ra and IL-10. Duration, intensity of exercise, muscle mass engaged during exercise, the muscular glycogen level and whether or not carbohydrate is ingested during the exercise determine the magnitude of the systemic IL-6 response. IL-6 inhibits lipopolysaccharide-induced TNF-alpha production in monocytes (Pedersen, 2019). Baseline of IL-6 serum reduced significantly after 2 weeks of moderate intensity Treadmill exercise in untrained young healthy males, reflected the potency of exercise to reduce the baseline inflammatory status in these subjects (Wulan et al, 2019).

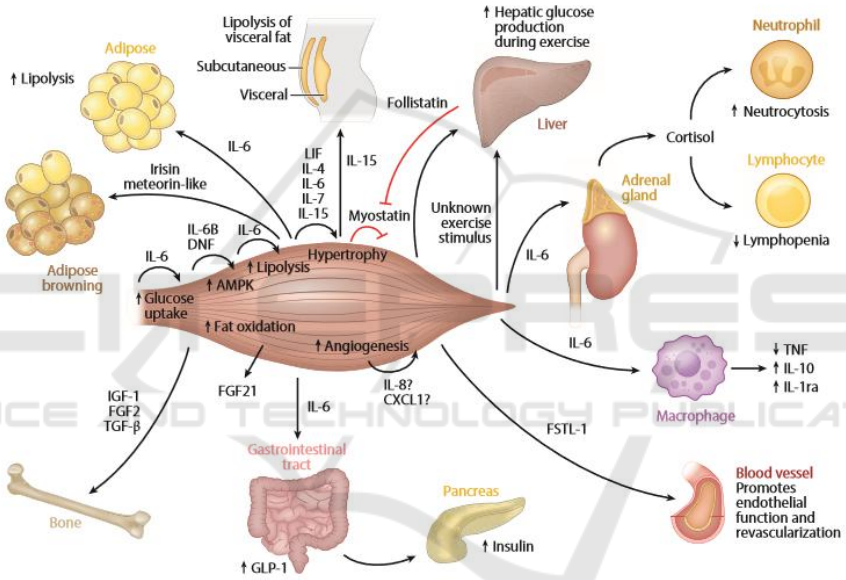

Figure 10: Skeletal muscle is an endocrine organ (Pedersen, 2019)

2.10 Adaptation Process of Physical Exercise

Exercise can reduce the immediate effects of stress and enhance the recovery process from allostatic load, as a role of fluidomechanic during muscle contraction as stated above (Teixeira et al, 2017. The dose response of exercise is very important thing and should be adjusted to achieve optimal exercise response, to meet the allostatic state demand. Depend on the exercise intensity, the body reactions can be classified as in the table 2 below. High activation state is the safe and efficient state to get benefit of the exercise for maintaining the fitness and health status, and we should pay attention carefully if the exercise is in overactivation state. It should be done in brief and be controlled to increase the toughness of body systems. The longer period of overactivation state would lead to more allostatic load, and reduce the survival capability of cells.

Table 2: Body Response to Exercise.

The influences of different NON-SPECIFIC REACTIONS on the body's state	BIOLOGICAL MEANING OF RESPONSE	METABOLIC PROCESSES STATE		WORKABILITY STATE	PMN NEUTROPHYL/ LYMPHOCYTE%
		ACTIVITY OF ANABOLIC & CATABOLIC PROCESSES	ENERGY EXCHANGE		
TRAINING	Cutting off nonessential, weak repetitive stimuli by developing a **protective inhibition in the brain**	Not high with prevalence of **anabolic processes**	Energy substrate accumulation exceeds energy expenditure, thus **energy is stored**	Workability level is **low** in **speed** but it is **good** in **working time**	0.27-0.52
CALM ACTIVATION	↑ activity of **control systems** of the body	↑ with prevalence of **anabolic processes**	**High-speed metabolism** of energy-supplying substrates, **well-balanced** by their expenditure and replenishment	Workability level is **high** both in terms of **precise execution, operation speed** and **duration of working**	0.45-0.64
HIGH ACTIVATION	↑ the activity of **control and protective systems** of the body	↑↑ with a **significant** prevalence of **anabolic processes**	**High-speed metabolism** of energy-supplying substrates, **well-balanced** by their expenditure and replenishment	Workability level is **high** in **precise execution and operation speed** and **some lower** in **duration of working**	0.70-1.12
OVER-ACTIVATION	An attempt to **retain the activation** response without falling into stress	**↑↑ and tense without prevalence**	Expenditure of energy-supplying substrates grows and their **replenishment gradually lags** behind	Workability level is **high**, however there may be **breakdowns activity**	0.45-1.12
STRESS	**Prevention of >> reaction** of the body that could result in death	↑↑ with prevalence of **catabolic processes**	Expenditure of energy-supplying substrates is sharply increased, their **replenishment is ↓**. Increasing the proportion of **glycolytic processes**	Workability level in **speed** can be **high at the beginning, but then it falls**. Workability level in **accuracy and duration of working is ↓**	0.07-0.31

3 CONCLUSION

Human body underwent the changes in every time and situations, which can help the body system to surpass the stress condition. For maintaining normal body function, toughness of physiological response is very important factors. Exercise is a nice orchestration of muscle contraction and fluidomechanic to activate the cellular to organ system for giving the best response to every change and prevent the body from adaptation failure (injury or disease).

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