Aging considerations

Aging is a usual life course that includes all physiological systems, seen as an advanced biological degeneration and decrease in physical capacities that raises the possibility of disease. Aging is a gradual decline of various organ functions of the body, deteriorating phenomenon defined by relations between the genetic expressions and external factors [1]. Ecological epigenetics defines how natural factors affect cellular epigenetics and, thus, human performance [2]. Aging is a multifaceted process that not only involves the natural biological processes of aging, but also the increased risk for different diseases such as coronary heart disease, diabetes and cancer [3]. The primary aging course, itself genetically related, occurs both independently of lifestyle and in the absence of disease [4]. Aging causes structural changes and functional decrements in skeletal muscles (sarcopenia), bone mineral density, cardiovascular and oxygen delivery. Age-related declines are manifest by a decreased ability for aged skeletal muscle to respond to physiological loads such as muscle loading or acute injury. Indeed, older adults often exhibit an age-related reduction in the number and size of muscle fibers, known as sarcopenia [5]. Accordingly, at maximal effort decreases in maximal cardiac output, arteriovenous oxygen difference and maximal oxygen uptake are noted [6,7]. These age modifications are the balance between cellular impairment due to metabolic measures happening inside the cell and offsetting molecular responses that can restore the damage. It is widely accepted that aging is an important risk factor for the development of hypertension and atherosclerosis with its vascular complications. The underlying mechanism whereby aging elevates the probability of disease onset remains obscure; however, it is likely closely related to underlying mechanisms of atherogenesis, the most accepted being the oxidation hypothesis [8]. In brief, a
vital phase in the progress of atherosclerosis is oxidative alteration of low-density lipoprotein. The oxidation of low-density lipoprotein is a free radical driven lipid peroxidation process and the aldehyde products of lipid hydroperoxide breakdown are responsible for the modification of the low-density lipoprotein a protein [9].

Successful aging is a function of both genetic and environmental factors [10]. The primary aging process, which is genetically associated, occurs both independently of life style and in the absence of disease [7]. Aging-related changes occur mainly in the cardiopulmonary and skeletal muscles, bringing about a reduction in physical performance [11]. Maximal work capacity is decreased regardless of lifestyle because of genetic factors. Such consequences contribute to the geriatric syndrome of frailty, thereby severely limiting the function, quality of life and longevity [12].

Muscle mass decreased significantly in aged individuals, after the sixth or seventh decades of life, [13].

This reduction in muscle mass is a major factor in the decline of maximal oxygen uptake, indicating the cardiopulmonary fitness of the individual [14], and therefore, bringing about a reduction in physical work capacity [11]. Such myocardial and peripheral functional changes include a decline in the maximum heart rate, stroke volume, and left ventricular contractility, and an increase in total peripheral resistance. Consequently, oxygen delivery to the working muscle decreases. The human population aged from 0 to 91 years screened previously by ELISA revealed that the level of s-Klotho was related to human physiological declines with aging [15].

Oxidative Stress

Oxidatively altered low density lipoproteins cause lipid-laden macrophage, or foam cell, buildup in the fatty strip, an atherosclerosis process begins. Following employment of immune cells, a pro-inflammatory stage, raises oxidative stress, and starts a sequence of actions including apoptotic vascular and nonvascular cells [16]. It has been suggested that up to 2% of the oxygen utilized (hyperoxide) in the cell’s mitochondria may produce oxygen radicals and peroxisomal level to increase, which may hit and alter DNA, protein, cell membranes and organelles as well as extracellular components [17]. Peroxosomal disorders are inherited diseases representing a group of genetic diseases in humans in which there is a lack of one or more peroxisomal functions [18].

Peroxisomes known as a microbody are organelles containing peroxide enzymes and have distinguishing assignments such as fatty acid’s breakdown [19]. Peroxisomes are found mainly in the liver and the kidneys, the organs mainly responsible for removing toxic chemicals. Peroxinsome carries out oxidation reactions, producing the toxic hydrogen peroxide (H2O2). In addition, peroxisomes hold the enzyme catalase, which causes toxic H2O2 elimination by converting it to H2O and O2 [20]. Peroxiosomes as well, is important for energy metabolism and is involved in the enzymatic activity of the pentose (5-carbon sugars) phosphate pathway. It is a metabolic pathway producing nicotinamide adenine dinucleotide phosphate (NADPH) and pentoses as well as ribose 5-phosphate, the last one serves as a precursor for the synthesis of nucleotides [21].

Hyperoxide as reactive oxygen species (ROS) is a chemical reactive molecule that contains the superoxide anion, such as peroxides and superoxide [22]. Superoxide is biologically relatively toxic and is arranged by the immune system to eliminate attacking pathogens. Superoxide is produced in large quantities by the enzyme NADPH oxidases [23]. With aging, peroxisomes may boost the production of ROS during cell metabolism Thus, hastening the aging process [24]. In addition, macro-autophagy process declines along aging, resulting in structures changes causing decrease in cell functions abilities [25]. Endothelial dysfunction is usually represented by dysregulation of the arterial normal smooth muscle contractile response, it contributes to the employment of immune cells and the pro-inflammatory stage. Oxidative stress induces endothelial dysfunction, following an elevated in its values, endothelial dysfunction stimulates the atherosclerosis pathological process. In addition, increased oxidative stress is a key factor in the progression of aging-related decreases in cell’s normal function [26]. Thus, prooxidant causes atherosclerosis, apoptotic and cell senescence relevant to aging process.

Exercise in aging

It has been suggested that exercising aged individuals keep high level of endurance capacity [27], meaning: exercising at intensities above the anaerobic threshold. There are growing evidences from; longitudinal and cross-sectional studies that chronic endurance training attenuates the decline in maximal oxygen uptake associated with age [7]. In addition, the position of aerobic exercise as a tool to reduce the risk of numerous long-lasting deteriorating diseases has been convincing recognized earlier [28,29] Also, improved physical work capacity following training may be consider as an accurate indicator of regular physical activity. Improved work capacity includes different physiological system mechanisms in the: cardiopulmonary capacity, body composition, muscular strength and endurance capacity.

Untrained and trained elderly can increase the response of the cardiopulmonary without a significant reduction in peripheral ability to extract oxygen at the muscle level. It was found that in elderly subjects, skeletal muscle mitochondrial capacity, tissue blood flow capacity, and oxygen exchange capacity appear to be well matched. It seems that intrinsic mitochondrial function and regulation are not altered significantly. Therefore, the higher aerobic capacity in the trained elderly is related to increases in the abilities of cardiovascular factors following training and to the lesser extent to increases in muscle mitochondria concentration and capillarity [30].

Both, anaerobic exercise and aerobic exercise generate ROS differently. Increase aerobic exercise intensity along with oxygen uptake results in ROS rise affecting, muscle contractile, and decreases oxidative damage, as long as exercise intensity is up to 75% [31]. One has to imagine the potential of 2% of an individual to produce peroxisomal following a fitness session lasting 60 minutes run with an oxygen uptake of 180 L02. During aerobic exercise ATP production is in the Krebs cycle with oxygen presence, where free fatty acids are the main source of energy production. Anaerobic exercise on the other hand, utilizes the glycolytic
pathway producing ATP and lactate. Aerobic exercise compared to anaerobic exercise produce larger ROS amount, however, anaerobic exercise induces continually ROS production during recovery. High blood lactate levels possibly has an effect on the increase ROS production by equine polymorphonuclear leukocytes involved in the pathogenesis, which relates to alterations in essential immune functions within a short period after all-out-intensity exercise [32]. Although more oxygen is consumed during aerobic exercise, the generated ROS does not induce significant oxidative damage. Oxygen uptake as such may not be the major cause of exercise-induced oxidative damage.

Metabolite peroxisome produced by the mitochondria during the energy production process, is modified by aerobic exercise in the redox setting. The peroxisome proliferator activated receptor (PPAR) γ coactivator 1-α (PGC-1α) a lipid catabolism and mitochondrial function regulator [33]. PGC-1α-activation could result in decreased oxidative challenge, either by upregulation of antioxidant enzymes and/or by an increased number of mitochondria that allows lower levels of respiratory activity for the same degree of ATP generation. Usually, Oleic acid a monounsaturated fatty acid, initiates 02- production through NADPH oxidase. However, oleic acid also, can alter cell’s reactive oxygen species (ROS) production. Oleic acid slows down electron’s sequence of reactions between the cytochromes within the Krebs respiratory chain and thus, due to their protonophoric act on the inner mitochondrial membrane by translocating, protons across lipid bilayers so, it significantly reduces ROS production in the converse mode of electron transport. These effects of oleic acid can modulate signaling functions of ROS, and thus, decrease apoptotic process of cells [34].

The oxidative activity of ROS is a normal function of cellular respiration but can impair the normal functioning of other molecules and systems if present in high amounts [35]. The body has natural antioxidant systems that help to keep ROS levels normal, however, these antioxidant systems can be overwhelmed, causing an acute accumulation of ROS known as oxidative stress[36]. Study by [37] tested the hypothesis that long-lasting aerobic exercise training could prevent the age-associated reduction in s-klotho serum levels, in thirty healthy sportsmen: 15 young aerobically well-trained elite athletes and 15 aerobically well trained master athletes. This study demonstrated that circulating s-Klotho levels are similar for young healthy well-trained elite runners and elite master athletes. This suggests that the response of s-Klotho depends on the aerobic fitness level [5,38]. In addition, levels of s-Klotho were significantly higher in both exercising groups when compared with age matched untrained subjects reported earlier by [39], suggesting that long lasting aerobic training may be an appropriate model for mechanistically probing the role of physical activity on s-Klotho expression.

S-Klotho

Klotho is a transmembrane protein that, also effects and control over the connection of humans to insulin and seems to be associated to as an anti-aging function [40]. The α-Klotho gene is highly preserved in humans and circulates in blood as s-Klotho which acts by way of a humoral factor [41]. In humans, serum levels of s-Klotho decrease with aging progress [42], that may be observed in patients with several aging-related diseases such as coronary artery disease, cancer, hypertension, and kidney disease [43,44]. The klotho gene encodes a single-pass transmembrane protein that binds to multiple fibroblast growth factor receptors and functions as a co-receptor for FGF23, a bone-derived hormone that suppresses phosphate reabsorption and vitamin D biosynthesis in the kidney [45]. In addition, the extracellular domain of s-Klotho protein is shed and secreted [46]. It has previously been demonstrated that Klotho protein increases the ability of cells to remove damaging ROS by increasing the cell functions that detoxify harmful ROS [47,48], however, the precise mechanism of klotho’s action is not fully understood, but it changes cellular calcium homeostasis, by both increasing the expression and activity of transient receptor potential cation channels, vaniloid subfamily, member 5 (TRPV5) which plays a key role in active Ca++ reabsorption in the kidney and decreasing that of transient receptor potential canonical 6 (TRPC6), a subtype of calcium-permeable channel [49]. Additionally, Klotho increases membrane expression of the inward rectifier ROMK1 channels i.e. renal outer medullary K+ [49,50].

Klotho-deficient mice show increased production of vitamin D and altered mineral-ion homeostasis is suggested to be a cause of premature aging like phenotypes, because the lowering of vitamin D activity by dietary restriction reverses the premature aging like phenotypes and prolongs survival in these mutants. These results suggest that aging like phenotypes were due to Klotho-associated vitamin D metabolic abnormalities [51,52]. The Klotho protein deficiency is known to participate in premature aging. Klotho protein contributes in numerous pathways that control aging, for example; phosphate homeostasis, insulin signaling and Wnt signaling regulation [53]. As an aging suppressor, Klotho is an important molecule in aging processes and its overexpression results in longevity [53]. The Klotho gene encodes a transmembrane protein that after cleavage is also found as a secreted protein. However, previously it has been shown that the circulating s-Klotho levels are significantly higher than the membrane-bound form in humans and mice and the latter is significantly higher than the former [53]. Importantly, its overexpression suppresses insulin/IGF-I signaling and thus extends the lifespan. In addition, Klotho participates in the regulation of several other intracellular signaling pathways, including regulation of FGF23 signaling, cAMP, PKC, transforming growth factor-β (TGF-β), p53/p21, and Wnt signaling [45,54, 15], studied, a population-based longitudinal study, revealed that low plasma levels of Klotho are associated with decreased activities of daily living in older individuals. In older community-dwelling adults, plasma klotho is an independent predictor of all-cause mortality [55]. Low plasma Klotho levels have also been associated with a poor muscle strength in older, community dwelling adults [56].

Summary

So far, the present review, suggests that aerobic exercise increase Klotho gene expression, thus may be a biological and harmless tool to slow down the aging process and various aging-related diseases. In addition, it has been shown that moderate
aerobic exercise possibly may increase Klotho gene expression in muscle cells and decrease ROD production [56]. However, others suggested lower aerobic intensities as a way to reduce ROS [39]. Following aerobic exercise training, expression of the membrane-bound Klotho protein levels was suggestively decreased pointing that membrane-bound Klotho protein compared to the secreted form may be the active one.

**Conclusion**

The present review suggests that aerobic exercise delays aging process by increase Klotho gene expression, which in turn, reduces ROS damages to the cell. The relationships between the circulating s-Klotho levels a potential anti-aging factor and aerobic exercise are beneficial to physically active aged individuals.

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**Conflict of Interest**

No conflict of interest.

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