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The effects of aerobic and anaerobic exercises on circulating soluble-Klotho and IGF-I in young and elderly adults and in CAD patients

Moran S Saghiv[1], D Ben Sira[2], E Goldhammer[3], and M Sagiv[2]

Abstract

Different studies support the notion that chronic aerobic exercises training can influence the circulating levels of soluble-Klotho (s-Klotho) and insulin-like growth factor 1 (IGF-I). The effects of s-Klotho include improving the quality of life, alleviating the negative impact of age on the body's work capacity, and possibly increasing longevity. This review provides an overview of the latest findings in this field of research in humans. The different modes of dynamic exercise and their impact on circulating levels of s-Klotho and IGF-I in young adult athletes, untrained young adults, trained healthy older adults, untrained healthy older adults, and coronary artery disease (CAD) patients are reviewed and discussed. Together these findings suggest that long-lasting (chronic) aerobic exercise training is probably one of the antiaging factors that counteract the aging and CAD process by increasing the circulating s-Klotho and lowering the IGF-I levels. However, following anaerobic exercise training the opposite occurs. The exact metabolic and physiological pathways involved in the activity of these well-trained young and master sportsmen should be further studied and elucidated. The purpose of this review was to provide a clarification regarding the roles of s-Klotho and intensities and durations of different exercise on human health.

Keywords

Aerobic exercise, epigenetic, aging, anaerobic exercise, coronary artery disease, master athletes, elite athletes

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Introduction

Exercise training can alter gene expression patterns (epigenetic) and the physiological responses at rest and during exercise.[1] Recent studies show that even brief exercise alters gene expression, and the pattern of change involves diverse genetic pathways, consistent with a global danger-type response, for a range of physiological functions from inflammation to tissue repair that would be useful following a bout of physical activity.[2] Physical exercise offers an epigenetic tendency with benefits in several health domains. Yet, it is only recently that regular exercise has begun to be interpreted as a positive epigenetic mechanism to modify the genome-wide DNA methylation patterns in humans.[1] This is achieved by helping to improve the work capacity and physical performance of humans in health and disease.[3] Since aerobic exercise increases the circulating levels of soluble-Klotho (s-Klotho), the Wnt-signaling transduction gets suppressed, and thus inhibiting cell senescence and preserving stem cells.[4] However, the precise mechanism underlying the aerobic exercise–induced

[1] Exercise Physiology Department, University of Mary, Bismarck, ND, USA
[2] Life Sciences Department, Wingate College, Wingate, Israel
[3] Heart Institute Bnai-Zion Haifa Medical Center, Technion Institute, Haifa, Israel

Corresponding Author:
Moran S. Saghiv, Exercise Physiology Department, Casey Center, Room 141B, University of Mary,7500 University Drive, Bismarck, ND 58504, USA.
Email: mssaghiv@umary.edu

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increase in s-Klotho secretion following 12 weeks of moderate aerobic exercise training or the elevation in insulin-like growth factor 1 (IGF-I) following anaerobic training remains unclear.[5] The benefits of exercise intensity are positive epigenetic changes in terms of mitochondrial biogenesis.[6] In addition, exercise training is widely appreciated for its effects on the cardiovascular and musculoskeletal, endocrine, and immune systems. Many of the benefits of exercise training, such as volume overload (such as aerobic exercise) and load overload (such as anaerobic activities), diminish within 2 weeks if physical activity is substantially reduced and disappear within 2–8 months if exercise training is not resumed.

s-Klotho

Klotho is a transmembrane protein that, in addition to other effects, provides some control over the sensitivity of the organism to insulin and appears to be involved in aging.[7] Klotho is highly expressed in the brain, kidney, parathyroid, and pituitary glands but also serves as a circulating hormone by which shedding forms s-Klotho which in turn can be detected in blood, cerebrospinal fluid, and urine.[8] The *α-Klotho* gene is highly conserved forming s-Klotho, a blood circulating protein to be highly conserved across species. In humans, the serum levels of s-Klotho decrease after 40 years of age. Age-related declines are manifested by a decreased ability for aged skeletal muscle to respond to physiological stimuli 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.[9] This decrease in blood s-Klotho levels may be observed in patients with several aging-related diseases such as coronary artery disease (CAD), cancer, hypertension, and kidney disease.[10,11]

The *Klotho* gene encodes a single-pass transmembrane protein that binds to multiple fibroblast growth factor (FGF) receptors and functions as a co-receptor for FGF23, a bone-derived hormone that suppresses phosphate reabsorption and vitamin D biosynthesis in the kidney.[12] In addition, the extracellular domain of s-Klotho protein is shed, potentially functioning as a humoral factor of Klotho protein.[13] The action mechanism of Klotho is not fully understood, but it changes cellular calcium (Ca) homeostasis, by increasing the expression and activity of transient receptor potential cation channels, vanilloid subfamily, member 5 (TRPV5) which plays a key role in active Ca^{++} reabsorption in the kidney, and by decreasing the expression and activity of transient receptor potential canonical 6 (TRPC6), a subtype of calcium-permeable channel.[14] Additionally, Klotho increases membrane expression of the inward rectifier Renal Outer Medullary (Potassium Channel) Kinase 1 (ROMK1) channels, that is, renal outer medullary K^{+}.[14,15]

Klotho-deficient mice show increased vitamin D production, 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.[16,17]

The Klotho protein deficiency is known to cause premature aging. Klotho is an important molecule in aging processes and its overexpression results in longevity.[18] The *Klotho* gene encodes a transmembrane protein that after cleavage is also found as a secreted protein. Importantly, its overexpression suppresses insulin/IGF-I signaling and thus extends life span. In addition, Klotho participates in the regulation of several other intracellular signaling pathways, including regulation of FGF23 signaling, Cyclic Adenosine Monophosphate (cAMP), Protein Kinase C (PKC), transforming growth factor-β (TGF-β), p53/p21, and Wnt signaling.[12,18]

Crasto et al.[19] in 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.[20] In older, community-dwelling adults, low Klotho levels in plasma have also been associated with a poor muscle strength.[21]

IGF-I

IGF-I, also called somatomedin C, is a cellular and secreted growth factor critical for normal body growth, development, and maintenance, and plays important roles in multiple biological systems.[22,23] IGF-I is an endocrine and autocrine/paracrine growth factor with major effects on development, cell growth and differentiation, and tissue repair, and it circulates at high levels in the plasma and is expressed in most cell types.[24] A variety of cellular responses are induced by IGF-I, including cell proliferation, differentiation, migration, and survival.[25,26] These cellular responses have implicated IGF-I in several conditions such as the pathophysiology of several cancers,[27] the mitogenic and myogenic processes during muscle development, regeneration, or hypertrophy, since, unlike other growth factors, IGF-I acts as both a mitogen and a differentiation factor.[28]

IGF-I is an important factor that regulates a variety of cellular responses in multiple biological systems. The *IGF-I* gene comprises a highly conserved sequence and contains six exons, which give rise to heterogeneous mRNA transcripts by a combination of multiple transcription initiation sites and alternative splicing. Several protein synthesis and degradation pathways are mediated by IGF-I, which act on the cellular and molecular levels to increase or reestablish the strength, and function of muscle fibers.[29]

Deficiency of IGF-I in skeletal muscle may contribute to sarcopenia by severely influencing protein synthesis. IGF-I has anabolic effects on muscle protein content by inhibiting protein degradation and promoting myogenesis. Thus, IGF-I attrition in skeletal muscles is associated with less protein

synthesis and muscle sarcopenia,[30] stress, and inflammation.[31,32] IGF-I is generally thought to be associated with positive attributes such as growth, health, young look, and well-being, yet the bulk of the scientific evidence suggests that signaling through IGF-I and insulin receptors is related to a shortened life span in adults.[33] Indirect data have supported the concept that IGF-I may be atherogenetic because it can induce vascular smooth muscle cell proliferation in vitro.[34] Thus, IGF-I has been considered a promoter of arterial obstructive lesions.[35]

Exercise training, s-Klotho, and IGF-I in healthy subjects

Regular participation in physical activity and/or exercise training programs can minimize the physiological alterations that occur during aging and may contribute to improvements in health and well-being.[36] When elite athletes engaging in various sports are analyzed, their mortality is lower than that of the general population.[37] Thus, long-term moderately vigorous and vigorous exercise training are associated with increased survival rates in specific groups of athletes and CAD patients.[38] There are several studies proving the definitive role of lifelong physical activity, which can be engaged in at any age,[39] even by those in their 80s or 90s.[40,41]. Accordingly, regular aerobic exercise promotes older adult health and disease prevention.[36]

Endurance exercise like biking, walking, swimming, and running results in longer life expectancy compared to anaerobic exercise like power lifting.[42] The limited data on humans to explore the association between exercise and s-Klotho drove others to explore the relationship between exercise training and plasma s-Klotho levels in mice.[43,44] As a first step to probe the connection between physical activity, age, and Klotho expression, Schefer et al.[43] quantified the effect of an acute exercise bout on circulating Klotho levels in mice. It revealed that acute aerobic exercise significantly increased the circulating Klotho levels. Avin et al.[9] evaluated in young and older sedentary women the change in circulating Klotho levels before and after completion of an acute aerobic exercise bout. It suggested that circulating Klotho levels are upregulated in response to an acute exercise bout but the response may be dependent on fitness level.

Saghiv et al.[45] tested the hypothesis that long-lasting aerobic exercise training could prevent the age-associated reduction in s-Klotho serum levels and increases IGF-I levels, in 30 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.[9,42] In addition, levels of s-Klotho were significantly higher in both groups, when compared with age-matched untrained subjects as reported earlier by Lee et al.,[46] suggesting that long-lasting aerobic training may be appropriate for mechanistically probing the role of physical activity on s-Klotho expression.

The human population from birth to 91 years screened previously by enzyme-linked immunosorbent assay (ELISA) revealed that the level of s-Klotho declines was with human physiological aging.[19] On the other hand, elderly with greater aerobic capacity have longer life expectancies compared to inactive people.[47] There are several studies proving the definitive role of lifelong physical activity, which can be initiated at any age.[39] Compared to sedentary young and old subjects, in the elite aerobic-trained young runners and master athletes, s-Klotho levels are markedly elevated, while IGF-I levels decreased.[48] IGF-I is generally thought to be associated with anabolism and well-being,[49] yet, signaling through IGF-I and insulin receptors is negatively related to adults.[50] A meta-analysis study indicated that increased circulating concentrations of IGF-I are associated with increased risks of colorectal, prostate, and premenopausal breast cancers.[51]

Another study on the association between s-Klotho serum levels and IGF-I levels in regular young adults and elderly subjects trained aerobically for their health and well-being[45] demonstrated that following aerobic training in young and elderly subjects circulating s-Klotho levels were found to be significantly higher compared to their untrained counterpartners. The cross-sectional study findings in young and aged individuals suggest that circulating s-Klotho levels increase in response to long-lasting aerobic exercise training and that the response depends on fitness level. A similar increase in circulating s-Klotho is also observed in response to an acute exercise in young and old mice, suggesting that this may be a good model for mechanistically probing the role of physical activity on Klotho expression in mammals.[9]

While in the aerobic-trained young runners and master athletes, s-Klotho levels were markedly elevated, IGF-I levels were decreased compared with sedentary young and old subjects.[48]

The comparative analysis of biochemical indices measured showed that the long-lasting aerobic exercise training causes the significant decrease in IGF-I concentrations, while no differences were noted in untrained subjects. This finding on the reduced IGF-I clarifies the results of a previously reported study[50] that it was impossible to determine whether exercise affects IGF levels. It seems that important methodological differences among studies, as well as concerns about study quality, limit the ability to draw firm conclusions in that abovementioned study. A meta-analysis indicated that increased circulating concentrations of IGF-I binding protein 3 (IGFBP-3) are associated with increased risks of colorectal, prostate, and premenopausal breast cancers.[51] Thus, it appears that s-Klotho is a protein that inhibits IGF-I and insulin receptor and IGF-IR signaling by inhibiting tyrosine phosphorylation of both receptors and their downstream signaling proteins.[52]

Anaerobic bouts can be limited by lactic acid levels in the blood and active muscles. It is characterized by exposing the subjects to a very high degree of sudden strenuous all-out exercise. Thus, the increase of IGF-I levels in the blood[53] was primarily due to a substantial major increase in plasma catecholamine concentrations.[54] In mice, anaerobic exercise bouts increase inhibition of weight gain and growth rate, which may result from exercise intensity and duration or frequency.[55]

While an association between aerobic exercise and s-Klotho expression has been previously suggested from longitudinal cohort studies,[19] a direct relationship between circulating s-Klotho and anaerobic exercise training has been recently investigated.[45] It revealed that levels of s-Klotho in aerobic-trained sportsmen were markedly higher compared to those measured in the anaerobic sprinters. These findings on long-lasting anaerobic exercise training suggest that circulating s-Klotho levels in sprinters are similar to those of sedentary young adult males[56] and that the response depends on aerobic fitness level.[42]

Following long-lasting aerobic exercise training, s-Klotho levels were markedly elevated and IGF-I levels reduced in the aerobic-trained sportsmen, while in the anaerobically trained sprinters, s-Klotho levels were significantly lower and had higher IGF-I. In the anaerobically trained athletes, the levels of s-Klotho and IGF-I were similar to those reported previously for sedentary young adults.[57] The reduced s-Klotho levels in the anaerobic sprinters may be associated in later life with increased mortality, increased rate of cardiovascular disease, and disability in daily living activities.[58,59]

A recent study on well-trained elite anaerobic sprinters tested on an aerobic bout[60] revealed a positive relationship between circulating plasma s-Klotho concentration and acute aerobic bout lasting 60 min, while the IGF-I levels reduced. However, in long-lasting well-trained elite aerobic athletes with high levels of circulating s-Klotho to begin with, an acute aerobic bout induced a slight increase in plasma s-Klotho concentration and a significant decrease in IGF-I levels.

It seems that the increase in the plasmas s-Klotho concentration, after 60 min of an aerobic bout in the anaerobic-trained athletes, might be responsible for the decreased IGF-I.

Exercise, s-Klotho, and IGF-I in aging

The primary aging process occurs both independent of life style and in the absence or presence of disease.[51,61] Aging is a complex multifactorial process that not only involves the natural processes of aging but also the increased risk of different diseases—coronary heart disease, diabetes, and cancer.[62] Studies have demonstrated that when researchers adjust the genes in certain mice, yeast cells, and other organisms, they can almost double the life span of these mice. Therefore, successful aging is a function of both genetic and environmental factors.[63,64] Multiple age-related structural and functional changes are involved in skeletal, cardiac, and oxygen delivery-extraction ability during the human senescence, resulting in a significant decline in aerobic capacity and in the expression of a gene located on chromosome 13, *Klotho* gene a suppressor of the aging phenomena as well as the circulation of s-Klotho proteins.[65,66]

The Klotho protein deficiency causes premature aging. As an aging suppressor, Klotho is an important molecule in aging processes and its overexpression results in longevity. Due to many reasons, the insulin/IGF-I has been considered as a key pathway in aging research. Because Klotho induces IGF-I and insulin resistance, these findings appear to contradict the previous evidence of increased life span of dwarf mice with reduced IGF-I and insulin levels and enhanced insulin sensitivity. However, activation of signaling molecules downstream from IGF-I and insulin receptors is reduced in both Klotho and dwarf mice, suggesting common mechanisms of delayed aging.[67]

s-Klotho inhibits IGF-I and insulin receptor, IGF-IR signaling, by inhibiting tyrosine phosphorylation of both receptors and their downstream signaling proteins,[68] thus, increasing longevity in mice.[69] Moreover, it has been shown that the blockade of IGF-I signaling induced by s-Klotho increased resistance to oxidative stress, thereby improving survival.[70]

Because of genetic factors, work capacity decreases with aging regardless of the lifestyle. Consequently, the maximal oxygen uptake decreases. Such consequences contribute to the geriatric syndrome of frailty, thereby severely limiting the function, quality of life, and longevity.[71] Apart from genetic endowment, an individual must also interact with environmental factors associated with longevity. One of these factors includes maintaining high level of physical activity.[72] Chronic endurance training will attenuate the decline in maximal oxygen uptake associated with age.[61,73] In addition, antiaging effects have also been ascribed to aerobic exercise training.[67] An association between muscle function and s-Klotho expression has been previously suggested from longitudinal cohort studies.[23]

A direct relationship between circulating s-Klotho and IGF-I following aerobic exercise training has been recently investigated.[45] This study demonstrated that circulating s-Klotho levels are similar for young healthy well-trained elite runners and master athletes. It seems that the response depends on aerobic fitness level.[42] In addition, levels of s-Klotho were significantly higher in both groups when compared with untrained subjects as reported earlier.[46]

Since aging is an independent risk factor for age-related diseases and mortality, there are growing efforts in gerontology research to slow aging and extend healthy life span. The population aged from birth to 91 years screened previously by ELISA revealed that the level of s-Klotho declines with aging.[19] On the other hand, at any age, elderly individuals with aerobic capacity have longer life expectancies compared to inactive people.[39,47]

While in the aerobic-trained young runners and master athletes, the s-Klotho levels were markedly elevated and the IGF-I levels were decreased compared with sedentary young and old subjects.[48] The scientific evidence suggests that IGF-I signaling through IGF-I and insulin receptors is related to a shortened life span in adults.[50] In addition, a meta-analysis study indicated that increased circulating concentrations of IGF-I are associated with increased risks of colorectal, prostate, and premenopausal breast cancers.[51]

Exercise, s-Klotho, and IGF-I in CAD

CAD is a highly prevalent disease in the general adult population and is a major cause of death. Several clinical studies have suggested that *Klotho* gene exerts strong cardioprotective effects. s-Klotho has been proposed as a key regulator of the development of cardiovascular disease. In the few published clinical studies, an association between low levels of s-Klotho and the occurrence and severity of cardiovascular disease have been reported as well as a reduction in cardiovascular risk when levels were high.[74] Earlier, a relationship between low levels of s-Klotho and the occurrence and severity of CAD as well as a reduction in cardiovascular risk when they are high are observed.[74] Diverse studies suggest that alterations in the levels of this molecule may be associated with pathophysiological abnormalities that result in increased cardiovascular risk.[75] This protein is related to the attenuation of vascular calcification as well as prevention of cardiac hypertrophy. For instance, *Klotho* gene has been shown to protect against vascular calcifications in rodent models of CAD. While in humans without CAD, higher s-Klotho levels have been related to a lower incidence of mortality and CAD,[68,75] while low s-Klotho levels have been associated with increased arterial stiffness in chronic kidney disease patients.[63] Additionally, several experimental studies indicate that s-Klotho facilitates the maintenance of vascular homeostasis. s-Klotho improves endothelial dysfunction through promotion of nitric oxide (NO) production and mediates anti-inflammatory and antiaging effects such as suppression of adhesion molecules expression, attenuation of nuclear factor-κ B or inhibition of Wnt signaling, thus, limits Wnt-mediated cellular senescence.[76]

Aerobic exercise training increases resistance vessel sensitivity and maximal responsiveness to adenosine. This has been confirmed in dogs and miniature swine in vivo.[77] Aerobic exercise and *Klotho* gene expression could reduce the risk of cardiovascular events in patients with prior CAD, it may decrease the risk of mortality,[68,78] incidence, and severity of cardiac events.[79,80] Furthermore, in patients with CAD, exercise training improves endothelium-dependent vasodilatation both in epicardial coronary vessels and in resistance vessels.[81]

Patients with significant CAD present lower concentrations of s-Klotho as well as reduced expression of *Klotho* gene in the vascular wall. The exonic variant KL-VS was associated with the incidence of atherosclerotic vascular disease and CAD.[75]

Saghiv et al.[82] assessed the effect of chronic aerobic exercise training on s-Klotho serum levels and IGF-I levels in CAD patients following long-lasting aerobic exercise training. The study demonstrated that in aerobically trained CAD patients, circulating s-Klotho levels were significantly higher, while IGF-I were significantly lower compared to untrained CAD patients and their healthy untrained counterpartners. In trained CAD patients, these findings suggest that in CAD patients, circulating s-Klotho levels are augmented in response to long-lasting aerobic exercise training. The reduced s-Klotho levels observed in the untrained CAD patients[82] was similar to other premature vascular aging diseases, such as hypertension or diabetes mellitus.[75] Further support for a direct role of *Klotho* gene in vascular homeostasis comes from in vitro studies showing endogenous expression of *Klotho* gene in human vascular smooth muscle cells.[83]

Conclusions

Inflection of Klotho expression through aerobic exercise training represents an interesting relationship that may contribute to the explanation of the antiaging and anti-CAD effects of long-lasting aerobic activity. Both are factors that may promote upgrading capacities of the elderly, CAD patients and healthy young adult subjects. Accordingly, a long-lasting aerobically trained individual is associated with decreased risk factors and increased s-Klotho that clearly counteracts the action of IGF-I. Following anaerobic exercise training, there is no association with circulating s-Klotho; however, it is a potent stimulus to increase plasma IGF-I levels.

Declaration of Conflicting Interests

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