

Mini Review

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Circulating Soluble-Klotho, Exercise, and the Cardiovascular System

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Introduction

It has long been established that anaerobic and aerobic exercise both acutely and chronically influence the cardiovascular system, its capacity for work, efficiency, and more [1]. Furthermore, exercise has been identified as one of multiple means to decrease the occurrence of aging, and limit the symptoms assigned with the ageing syndrome [2].

The Ageing Syndrome

Often, aging (or ageing) is regarded as a syndrome. Aging has been addressed as a syndrome presenting with a group of clinical and non-clinical symptoms and processes that decrease or increase as one's age advances [3]. Olson CB suggested that aging is a multifactorial process [4] while de Magalhães JP (2004) suggested that aging originates and occurs at the cellular level [5].

S-Klotho

The Klotho gene was discovered in rats in the year 1997 by Kuro-o et al. [6]. Klotho has been identified a bit more than two decades ago as an ageing influencer (for better or for worse) [6,7]. While plenty of data exist regarding Klotho and S-Klotho in general, relatively few data exist regarding the mutual effects of exercise on S-Klotho and S-Klotho on exercisability. The Klotho protein has two forms: one as a membrane protein, and the other in secreted form [8]. The researchers reported the gene had several ageing suppressing properties. The researchers indicated that the gene encodes for a membrane protein with similarities in its sequence to those of enzymes from the beta-glucosidase family [6]. The protein was suggested as part of a signaling pathway that is

influential in age-related diseases' morbidity and the regulation of ageing in vivo [6]. Kuro-o et al. further indicated a defect in the gene may lead to a shorter lifespan, infertility, Arteriosclerosis, skin atrophy, Osteoporosis, Emphysema, and a syndrome resembling that of human ageing [6]. 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, and disease related effects [9,10]. Klotho gene expression is positively influenced by different exercise modalities acting as an epigenetic influencer [11], resulting in increased work capacity, performance, and lifespan, and decreased aging in healthy and diseased populations [12-14]. As is the case with exercise, positive adaptations decrease and diminish with time if exercise training is not maintained.

Exercise Modalities and S-Klotho

Regular aerobic exercise participation promotes health and disease prevention [15]. Endurance exercise such as biking, walking, swimming and running, appear to benefit longer life expectancy than anaerobic exercise such as power lifting [16]. It has been suggested that circulating S-Klotho levels are upregulated in response to an acute exercise bouts, but that the response may be dependent on a person's fitness level [17-20]. Compared to sedentary young and old subjects, in the elite well aerobic trained young runners and master athletes S-Klotho levels are markedly elevated while [21] IGF-I is generally thought to be associated with anabolism and wellbeing [22], yet, signaling through IGF-I and Insulin receptors is negatively related to adults [23].

S-Klotho and the Cardiovascular System

Several clinical studies have suggested that the Klotho gene exerts strong cardio-protective effects. S-Klotho has been proposed as a key regulator of the development of cardiovascular disease. An association between low levels of S-Klotho and the occurrence and severity of cardiovascular disease have been reported, as well as a reduction of cardiovascular risk when levels were high [24]. This protein is related to the attenuation of vascular calcification as well as prevention of cardiac hypertrophy.

Semba RD et al. [25] concluded that in community-dwelling adults, higher plasma klotho concentrations are independently associated with a lower likelihood of having cardiovascular disease [25].

Nagai R & Hoshino Y [26] reviewed the new knowledge (at the time of publishing their review) in regard to the genetics of cardiovascular disease. In their article they wrote "We recently found a novel gene which seems to affect human aging phenotype and vascular endothelial function. It is important as a future study to clarify the regulatory mechanisms of the klotho gene in the cardiovascular system and the clinical significance of klotho gene polymorphisms" [26].

Saito Y et al. [27] reported regarding Klotho's influence of human vascular endothelial tissue, suggesting it has a protective role. The researchers indicated the secreted form of Klotho is of cDNA, and the lack of knowledge as to its pathophysiological relevancy. In their conclusion the authors wrote "These results suggest that the Klotho protein protects the cardiovascular system through endothelium-derived NO production by humoral pathways" [27].

Skrzypkowska M et al. [28] suggested a possible mechanism explaining Klotho KL-VS polymorphism's influence on ageing and cardiovascular disease development. These researchers suggested that individuals possessing at least one KL-VS allele are characterized by greater number of CD34+ and CD34+VEGFR2+ and their various subpopulations (CD34+CD133+, CD34+c-Kit+, CD34+CXCR4+ and CD34+VEGFR2+c-Kit+) than wild-type". The researchers came to the conclusion that "One of the mechanisms that are responsible for previously described KL-VS heterozygote advantage may be connected with maintaining greater size of hematopoietic and endothelial progenitor cells population" [28].

Serum klotho was an independent biomarker of LVMI but not arterial stiffness and vascular calcification. Further studies are warranted to elucidate the clinico-pathogenic significance of klotho for cardiovascular parameters, and whether any interventions to maintain or increase the serum klotho level can prevent cardiovascular events and mortality in CKD patients [29].

S-Klotho, Exercise, and the cardiovascular System

The research of the relationship between exercise modalities and S-klotho in health and disease is on the rise. The combination of two research findings whereas S-Klotho had cardiovascular protective characteristics and that exercise modalities have an influence on S-Klotho levels, leads one to the logical conclusion that exercise will influence for the better one's cardiovascular clinical condition via increase of S-Klotho.

Saghiv et al. [30] concluded that "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".

In their conclusions Matsubara T et al. [31] wrote "a correlation between plasma Klotho concentration and arterial stiffness, as well as aerobic exercise capacity. Furthermore, aerobic exercise training increased plasma Klotho concentration and decreased arterial stiffness. The decrease in the arterial stiffness was associated with an increase in plasma Klotho concentration. These results suggest that aerobic exercise training induced an increase in plasma Klotho concentration, which in turn, could contribute to a decrease in arterial stiffness".

Conclusion

Both exercising, especially aerobically, and high levels of S-Klotho, decrease the chances of the occurrence of cardiovascular disease. Exercise increases the levels of S-Klotho, which in turn, decreases evermore the chances of cardiovascular disease.

Acknowledgement

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Conflict of Interest

No conflict of interest.

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