Aerobic Exercise and S-Klotho Effects on Cardiovascular Disease Patients: A Review

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Abstract

Coronary artery disease (CAD) is the most common type of heart disease progression once major coronary arteries are injured or diseased. When the primary blood arteries which supply the myocardium with blood, oxygen and nutrients is narrowed arterial disease progresses. Plaque buildup in the walls of the arteries from hypercholesterolemia (high blood cholesterol), dyslipidemia, and vascular inflammation contribute to atherosclerosis formation, a primary agent for CAD. Arterial stiffens occurs as a result of the biological aging process and arteriosclerosis. Endothelial dysfunction is characterized by reduced vascular nitric oxide levels. Nitric oxide vascular reductions leads to irregularities in blood artery function. These functional irregularities result from atherosclerosis, causing vasoconstriction of small arteries. Vasoconstriction of smaller arteries is related to hypertension and could possibly influence, left ventricle diastolic dysfunction. There are two forms of klotho; membrane and secreted, membrane klotho acts as co-receptor for fibroblast growth factor (FGF)-23, while secreted klotho (s-klotho) regulates nitric oxide production in the endothelium minimizing endothelial dysfunction. Studies examining the effect of aerobic exercise on blood circulating s-Klotho have demonstrated a fitness dependent response. S-Klotho values have been shown to be significantly higher in trained vs untrained individuals. Aerobic training is an appropriate model for mechanistically probing the role of physical activity on s-Klotho expression. Factors associated with endothelial function improvement; aerobic fitness levels and aerobic training increased s-klotho levels alleviate and attenuate endothelial dysfunction. Aerobic exercise and klotho gene expression is shown to reduce cardiovascular events in patients with prior CAD thereby decreasing mortality risk.

Keywords: Atherosclerosis; Nitric oxide; Reactive oxygen species (ROS); Endothelial dysfunction; Klotho; Coronary artery disease; Oxidative stress

Introduction

Cardiovascular diseases are prevalent in the general population and are the leading cause of death worldwide responsible for 46.2% of noncommunicable deaths [1,2]. Coronary artery disease (CAD) broadly comprises CAD myocardial infarction, vascular stiffening, and left ventricular hypertrophy [3]. CAD regularly advances over long periods and is the most common type of heart disease that progresses once major coronary arteries are injured or diseased. Arterial diseases progress once the main blood arteries that supply the myocardium and the different organs with blood, oxygen, and nutrients is narrowed. Inflammation and cholesterol that creates plaque in the arteries are the cause for arterial diseases [4]. Plaque buildup in the walls of the arteries from hypercholesterolemia, fatty deposits, other substances and inflammatory mechanisms combine dyslipidemia to atheroma development, are usually the main causes...
for CAD [5]. Once plaque is present, decrement in blood flow to the body’s organs occurs which in turn, decrease blood flow causing reduction in oxygen delivery to the tissues and thus, ischemia [6]. The additional arterial tension and subsequent damage due to hypertension cause the coronary arteries to become narrowed from accumulation of fat, cholesterol and other molecules that collectively is the slow process of chronic inflammatory disease [7].

Atherogenesis is the process of forming plaques in the intima layer of arteries. Plaque’s compositions include mainly fat, cholesterol, and calcium [8]. With time, arterial diameter narrows decreasing arterial blood flow. This progression is termed atherosclerosis. Thus, atherogenesis is a multifaceted interface of risk factors with cells of the artery wall, the blood, and molecular communications [9]. Initial atherosclerosis is the consequence of the endothelial cells in the intima layer capturing monocytes along with endothelial permeability aiding the low-density lipoprotein elements to drift into the arterial wall. Myocytes develop and become macrophages that consume the low-density lipoprotein units with apolipoprotein apoB molecule to form foam cells. Oxidative radicals oxidize the apoB molecule, assemble the units mainly designated to be phagocytized by macrophages [10].

Damage progression is the second stage where the migration of the smooth muscle cells from the arterial wall intima layer into the tunica intima. The next stage is the formation of thrombosis. The rupture of the thin cap fibroatheroma that covers the plaque plus the coagulation components of blood interact with the thrombogenic plaque produces thrombi [11]. In addition, risk factors such as, high cholesterol values, hypertension, diabetes, overweight and oxidative radicals affect the early phase of atherogenesis, namely endothelial dysfunction [12,13]. In brief, atherosclerosis develops progressively with inflammation and lipid accumulation. Atherogenesis is the course of creating plaques in the intima coating of arteries. The buildup of low-density lipoprotein and the inflammation of the arterial wall are the first phase of atherosclerosis. Atherogenesis results from lipid peroxidation-derived aldehydes oxidized to carboxylic acids. The pro-inflammatory oxidized phospholipids, resulting of the oxidation of low-density lipoprotein and phospholipids including arachidonic acid, formed in the lipooxygenase and myeloperoxidase pathways, these molecules attract and trigger inflammatory cells, such as monocytes, T-cells, and macrophages. Matrix degradation brings about atherosclerotic as a result of macrophages activation through; cytokines, reactive oxygen species (ROS), and proteolytic enzymes. Oxidative stress is also considered to be a key factor in mechanisms of changes in cell function [14], such as the aging process [15].

Klotho is an anti-aging gene with implications in biological and anatomical processes, mainly in cardiovascular disease [16]. Early human aging involving endothelial dysfunction, vascular calcification and progressive atherosclerosis were seen in mice lacking Klotho [17]. In addition, reduced Klotho levels is observed in coronary artery disease patients, physically inactive individuals and in aging, S-Klotho has a role in the action of fibroblast growth factor 23 (FGF23), which directly binds to FGF receptors (FGFRs). This, high affinity complex for FGF23 mediates the intracellular effects of metabolism of phosphorus as the required co-receptor [18]. Other mechanisms which s-klotho is involved, include reduce oxidative stress, inflection of inflammation or attenuation of vascular stiffening [19,20]. Therefore, Klotho has been suggested as a master regulator of cardiovascular disease [21].

Aerobic exercise and Klotho gene expression could reduce the risk of cardiovascular events in patients with prior coronary artery disease thus, aerobic exercise may decrease the risk of mortality, incidence and severity of cardiac events [12,15,22-24]. In addition, in patients with CAD exercise training improves endothelium-dependent vasodilatation both in epicardial coronary vessels and in resistance vessels [24] Patients with significant coronary artery disease present lower soluble concentrations of α-Klotho (s-Klotho) [25], as well as reduced levels of Klotho gene expression in the vascular wall [26]. This protein is related to the attenuation of vascular calcification as well as prevention of cardiac hypertrophy [27]. Reduced serum s-Klotho concentrations and decreased vascular Klotho gene expression were associated with the presence as well as the severity of coronary artery disease independently of other established cardiovascular risk factors [14,23]. S-Klotho is a pleiotropic protein related to longevity, which acts as a co-receptor of the fibroblast growth factor 23 and 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 of cardiovascular risk when levels were high [28].

**Arterial Endothelial Dysfunction**

Arterial endothelium assists vasomotor tone and function by producing and discharging nitric oxide [29]. Arterial endothelium is characterized by cells in the inner layer of all blood arteries and lymphatic system. The inner layer of arteries and veins is the tunica Intima. In arteries, this layer is composed of an elastic membrane lining and smooth endothelium which is a unusual type of epithelial tissue that is covered by elastic tissues. The small thickness of endothelium at the capillaries level permits molecules movements actively and passively as well as ions among blood and lymph by means of the tissues [30]. Following the endothelial layer, elastic fibers thickness varies, which is in a straight line associated to its ability to change vessels’ blood volume, pressure and flow velocity [31]. Arterial endothelium contributes to the regulation of blood coagulation, platelet and leukocyte action, vessel’s tone and inflammatory responses [32]. The endothelium
plays an important role in blood vessel functions by producing various signaling molecules [33]. It is a vital regulator of blood flow and blood pressure in the circulatory system. The endothelium is the internal coating of cells that has several critical functions, it controls the correct vessels’ radius namely; constriction or dilation, thus changing rapidly blood’s amount delivered to the various organs. The endothelium also protects the tissues from various toxic substances by: a. coagulation or formation of a fibrin dot, which is a mechanism that blood changes from a liquid to a gel, it includes activation, bond, and accumulation of platelets along with deposition and maturation of fibrin, b. controls the fluid, c. regulates electrolytes’ levels and, d. exchange of numerous substances between the blood and the tissues and Vic versa, and, e. regulates inflammation damages in the tissues. Consequently, Endothelium function is critical for the regular function of the arteries, tissues and organs [34].

Existence of hypertension and dyslipidemia are directly associated to endothelial dysfunction resulting inflammatory and arterial damage [35]. The coronary artery response to acetylcholine rest on the capacity of the endothelium and the endothelial nitric oxide pathway [36]. Arteriosclerosis affects the major elastic and muscular arteries in the extracellular intermediate of arteries elasticity resulting in arterial stiffens [37]. Arterial stiffens outcomes after a deteriorating course affecting mostly the extracellular medium of elastic arteries. It expresses the arterial wall viscoelastic capacity which affects arterial smooth muscle and therefore, the regulation of blood flow, blood pressure, arterial pulse, permeability, and inflammation [38,39]. Changes in extracellular medium proteins and mechanical properties of the arterial wall associated to vessel stiffening can trigger other mechanisms implicated in the progress of atherosclerosis. With time, arterial stiffness increases progressively, exposing the individuals to a greater pressure variation related to increased risk of stroke and renal impairment [40]. Changes in arterial pulsatile lead to an increase in the slow frictional force of blood flow counter to the vessel wall [41]. However, increased wall shear stress reduces nitric oxide production by the endothelial that in turn, increases rate of atheromasias (artery inflammatory) development [42,43]. During aerobic exercise training, systolic blood pressure increases thus, pressure in the artery wall rise resulting in the activation of the autoregulation mechanism and thus, vasodilation, that in turn, improves blood flow [44] and thus, has the potential to minimize these pathological process’ and to reduce the amount of cardiovascular complications [35].

Dysregulation of the nitric oxide normal smooth muscle contraction properties response is usually characterized by endothelial dysfunction, following advanced atherosclerosis and increase oxidative stress [45]. that induces endothelial dysfunction and atherosclerosis progression by reducing nitric oxide availability [46]. Endothelial dysfunction is a significant moderator in the progress of atherosclerosis and exist long ahead the creation of atherosclerotic plaques [47]. Endothelial dysfunction is mostly triggered by decreased production or action of relaxing mediators. At this point, it is clear that reduced nitric oxide levels cause endothelial dysfunction in blood arterial walls which, leads to vasoconstriction of the artery [48], and thus, increase blood pressure to high values (hypertension). In addition, it also, activates platelets leading to blood clotting, that increase the stimulation for artery walls inflammation, consequently, arterial walls penetrability to destructive lipoprotein, oxidized free radical species and various toxins is increased.

**s-Klotho**

α-Klotho protein is found extensively in human tissues of arteries, epithelium, endocrine system, and nerve tissues [49]. Molecular characteristic of Klotho is explained in detail by Martin-Nunez and colleagues, and therefore it is advised to the reader to look into this article [50]. Klotho appears in two forms; membrane and secreted, the membrane klotho acts as an necessitate co-receptor for fibroblast growth factor (FGF)-23, while secreted klotho regulates nitric oxide production in the endothelium. The extracellular domain of Klotho can be cleaved and cut in the circulation as s-Klotho where it may function as a blood vessel-protective hormone possibly by enhancing endothelial function [51,52] or, direct inhibition of arterial calcification [53]. Circulating s-Klotho is produced in the kidney predominantly expressed in renal distal tubular epithelial cells with implications in biological and anatomical processes, mainly in the cardiovascular arterial’s disease [16]. Early human aging that contains endothelial dysfunction, arterial calcification and progressive atherosclerosis were seen in mice lacking Klotho [17]. A reduction in Klotho levels is observed also in aged and physically inactive coronary artery disease patients [26]. These declines are demonstrated by a diminished ability for skeletal muscle to respond to physiological stimuli such as muscle loading or acute injury. Certainly, older adults often exhibit an age-related reduction in the number and size of muscle fibers known as sarcopenia [48]. Klotho appears to apply different functions in distinct cell types as nitric oxide-reliant means, Klotho is a putative anti-aging gene, vital cofactor for the linkage of fibroblast growth factor (FGF) 23 to its receptor, and thus, acting as a main controller of phosphate balance [18,54]. Studies on mouse genetics have revealed in vivo functions of Klotho (FGF signaling) [55,56].

The Klotho proteins and its connected enzyme β-Klotho apply various influences on the biological regulation of ion transport, energy metabolism, calcium and phosphate mainly by FGF-23 [57] In addition, s-Klotho functions as an obligate co-receptor with fibroblast growth factor receptor 1 (FGFR1) for fibroblast growth factor 23 (FGF23), a phosphaturic hormone essential for
maintaining mineral homeostasis [58]. Serum FGF-23 values are related to atherosclerotic problem, endothelial dysfunction, arterial stiffness and vascular calcification [59,60]. Therefore, Klotho has been suggested as a master regulator of CAD [20,61]. Klotho inhibited the phosphatidyl nitric oxide synthase 3-kinase (PI3K)-AKT signaling pathway phosphorylation of fork head box protein O3a by improving its connection to the manganese superoxide dismutase cofactor. Klotho increased mitochondrial manganese superoxide dismutase, mRNA and protein expression. In addition, Klotho reduce tacrolimus-induced oxidative stress and thus, reverse mitochondrial dysfunction, consequently, decrease ROS production [56]. Increased cellular levels of ROS result in damage to proteins, nucleic acids, lipids, membranes and organelles, which can lead to activation of cell death processes such as apoptosis. Mice with Klotho deficiency demonstrate an association with accelerated and enhanced development of atherosclerosis [62] and early aging. However, increased Klotho expression increase genetic expression that solve the Klotho-deficient phenotype at baseline [16] and thus, improve mice’s standing against oxidant stress [63]. In humans, serum levels of s-Klotho decrease after 40 years of age [25,64]. This may be observed in sedentary individuals and patients with several aging-related diseases such as cardiovascular disease, cancer, hypertension, and kidney disease [65,66].

The clinical relations of s-Klotho and cardiovascular diseases were described earlier [67,68] suggesting that, s-Klotho values in the circulating blood in CAD patients are significantly lower compared to healthy matched peers. In addition, in community-dwelling adults higher plasma Klotho concentrations are independently associated with a lower likelihood of having CAD, heart failure, stroke, or peripheral arterial disease. Recently study by Saghiv, et al. [68] demonstrated that circulating s-Klotho levels are significantly higher while IGF-1 are significantly lower in aerobically trained CAD patients compared to untrained CAD patients and inactive healthy counter partners. Genetic variation studies have demonstrated that Klotho gene polymorphisms might be associated with longevity on one hand [16] and CAD on the other hand [69-71]. Previously Arking, et al. [72] suggested that, the functional of KL-VS allele, characterized by six SNPs is related to hypertension and stroke, and thus, it is a self-regulating risk factor for CAD [73].

Atherosclerosis reduction and cell protection occur by some antioxidant’s such as s-Klotho humoral. In addition, arterial stiffening may predispose the intima to atherosclerosis due to injury sustained from increased pulsatile pressure. In mice, klotho through humoral pathways guards the arteries by nitric oxide produced in the endothelium [74]. The discovery of Klotho in human vessels tissue [75,76] increased the understanding about the role of the co-expression of two related FGF23 receptors, FGRF-1 and FGRF-3 [76]. Expression of Klotho protein seems to be restricted to arterial intima layer [78]. Yet an argument exists due to inconsistent data regarding Klotho presence in arterial tissue [79]. The connection of Klotho to endothelial dysfunction lays in the attenuation effect on endothelial dysfunction by ways of nitric oxide. Shimada, et al [80] suggested, that lack of nitric oxide decrease angiogenesis in k/kl mice and reduced endothelium-derived nitric oxide release, due to increased oxidative stress associated with aerobic exercise and aging. Klotho resists oxidative stress by the expression of manganese superoxide dismutase (Mn-SOD) through activation of FoxO forkhead also known as forkhead in rhabdomyosarcoma transcript factor [81] at the cellular and organismal level in mammals. FoxO forkhead is a human protein encoded by the FOXO3 gene [82]. FOXO3 belongs to the O subclass of the forkhead family of transcription factors which are characterized by a distinct fork head DNA-binding domain [83]. Klotho protein stimulates the FoxO forkhead transcription factors that are negatively regulated by insulin/IGF-1 signaling, so bringing about an expression of manganese superoxide dismutase. With this content, Klotho increases nitric oxide formation through c-AMP-PKA-dependent pathway in human umbilical vascular endothelial cells, [19] and decreases (HO2)-prompt apoptosis and cellular senescence [83].

In addition, Klotho reduces oxidative stress production by limiting angiotensin II production [85]. While the complete actions of angiotensin II signaling on NADPH oxidase are still under examination, angiotensin II, is an endogens peptide hormone, that has a major role in maintaining homeostasis in the cardiovascular system, as well as an effective stimulator of NADPH oxidase [86]. Recently, Six, et al. [87] observed that attenuation of FGF23 or phosphate-induced vasoconstriction mediated by Klotho is eliminated by adding nitro-L-arginine, a competitive inhibitor of nitric oxide. Moreover, they observed that exposure of human umbilical vein endothelial cells to Klotho increased nitric oxide production and induced nitric oxide phosphorylation and the inducible isofrom, nitric oxide, involved in immune response expression. Interestingly, Klotho was able to increase (HO2) production in cultured human vascular smooth muscle cells, which suggests a more complex effect of this protein on the regulation of vascular tone through mediation of a ROS/nitric oxide balance [87].

**Aerobic Exercise**

Physical inactivity decreases maximal oxygen uptake, muscle mass (sarcopenia), alters structural and intrinsic muscle cells and changes in energy availability which, decrease further with aging [88,89]. Cardiac patients in a stage of myocardial deficiency usually lose their muscle mass and muscle strength, due to angiotensin II that directly affects the skeletal muscle and increases protein degradation [90]. Skeletal muscle atrophy is categorized by a reduction in protein contented, fiber width, force generation, and tiredness struggle ability [88]. In addition to angiotensin II, factor such as ROSs cause muscle protein degradation under different situations [88]. The existence of muscle atrophy points out of the
Exercise training intensifies nitric oxide production, that improves cardiovascular risk factors [106]. The nitric oxide synthesis rate seems to be parallel related to increase in amino acid arginine availability [107]. The anti-thrombotic effect of aerobic exercise decreases serum levels and activity of inflammatory factors, such as interleukin-6, C-reactive protein, and tumor necrosis factor-α, pointing out about the anti-thrombotic effect of aerobic exercise [108]. Following aerobic bout, blood pressure decreases to lesser levels than those recorded at rest, identified as post exercise hypotension [109]. This autoregulation mechanism response of aerobic exercise coupled with the nitric oxide vasodilator, affects positively the endothelium function and thus blood flow by decreasing total peripheral resistance [110, 111].

Although the association between s-Klotho and aerobic exercise training is not clear; recently, the α-Klotho gene is circulating in blood as s-Klotho have been related to the aerobic exercise [112,113]. Yet, exercise appears to take a major part on the secreted form of the α-Klotho gene in humans. In addition, α-Klotho gene is associated also with genes: β-Klotho gene and γ-Klotho gene, however, the last two mentioned genes do not have any role during exercise [114]. The increase in s-Klotho following aerobic exercise training may be a response to ROS that increase in muscle cells as a result of aerobic training, s-Klotho reduces apoptosis through the nitric oxide production and thus, suppress oxidative stress [115].

**Interplay between Exercise, S-Klotho and Endothelial Dysfunction**

Data suggests that endothelium plays a major part in the regulation of arterial stiffness by the action on smooth muscle tone affected by vasoactive intermediaries and, the effect of nitric oxide production on endothelin arterial stiffness [116]. Nitrogen nitric oxide is a soluble gas molecule with the chemical formula for NO. It is continually synthesized by the endothelium: L-arginine in endothelial cells is the precursor for nitric oxide synthesis by calcium-calmodulin-dependent enzyme nitric oxide synthase [117]. Nitric oxide acts as an endothelium-derived relaxing factor [118], released from endothelial cells and acts as an inhibitor of ROS production, by decrease in L-arginine endogens asymmetric dimethyl-L-arginine ratio connected with endothelial dysfunction [119]. Nitric oxide stimulates phospholipidase A2 and inhibitors of lysolecithin acyltransferase inducing smooth muscle tone relaxation by inhibiting low density lipoprotein oxidation [120]. Klotho has been linked to the prevention of muscle atrophy and cardiovascular disease in aged individuals [14]. Circulating s-Klotho acts as a humoral factor, involved in the endothelium production and regulation of nitric oxide. In turn, nitric oxide protects endothelial...
penetrability, smooth muscles’ contraction by calcium homeostasis and inhibits insulin-like growth factor-1 signaling [121].

Similar to Klotho's anti-aging impacts have also been attributed to aerobic exercise [114, 122]. In recent years, there are enough studies regarding the effect of aerobic exercise on blood circulating s-Klotho [23, 67] Reimers, et al. [123] demonstrated that the response of s-Klotho depends on aerobic fitness level. In addition, levels of s-Klotho were significantly higher in trained individuals compared to untrained once [124], suggesting that long lasting aerobic training may be an appropriate model for mechanistically probing the role of physical activity on s-Klotho expression. Populations aged 0 - 91 years, screened previously by ELISA revealed that the level of human s-Klotho declines with aging [125]. Previously in older mice, it has been demonstrated that low blood serum s-Klotho levels are related to reduced skeletal muscle strength and aerobic capacity [126]. On the other hand, trained elderly with aerobic capacity have longer life expectancies [127] and higher serum s-Klotho values compared to inactive elderly [112].

Moderate aerobic training attenuates aging-induced pathological cardiac hypertrophy at least partially by restoring s-Klotho levels, reduce oxidative stress, and lessening in the phosphorylation of ERK1/2, P38 and fibrosis [128]. The relationships between aerobic exercise, s-Klotho and endothelial dysfunction can be in brief described as follow: previously it has been suggested that s-Klotho and long-lasting aerobic exercise training are factors that may promote and upgrade young adults’ physical performance capacities [129]. Aerobic bout increases s-Klotho levels which in turn, increase FGF23 which promotes nitric oxide synthesis bringing about a reduction in oxidative stress and ROS in skeletal muscle and accordingly, increase mitochondrial vitality and thus [130] attenuate restore endothelial dysfunction.

Conclusion
Recent developments point out on the effect of aerobic exercise training program as nitric oxide nonpharmacological mean to support in the treatment, prevention, and therapy of patients with cardiovascular diseases. The present review, suggests that aerobically active CAD patients, increase their Klotho gene expression, which may be a primary involvement to slow down endothelial dysfunction course and cardiovascular-related diseases. In addition, moderate aerobic exercise increase Klotho gene expression in muscle cells and decrease ROD production. Future research should examine the relationship between aerobic exercise training and circulating s-Klotho, on cardiovascular arterial stiffness and endothelial dysfunction.

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Conflict of Interest
No conflict of interest.

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