Vascular Calcification Regulated by Klotho During Physiological and Pathophysiological Aging

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SUMMARY

Purpose: The widely spread membrane and soluble Klotho protein plays a pivotal role in vascular calcification by orchestrating calcium/phosphate/magnesium homeostasis mediated by the Klotho/fibroblast growth factor 23 receptor complex. Our aim was to review new scientific data and discuss the role(s) of Klotho in vascular calcification.

The basic procedures were to review the literature concerning Klotho and its mechanisms of action during physiological and pathological aging.

Main findings: A lack of Klotho shortens the lifespan, increases vascular calcification and the frequency of cardiovascular diseases with multiple organ degeneration and weakness in experimental animal models. In humans, the most prominent decrease of Klotho protein and mRNA is found in patients with chronic kidney disease–mineral and bone disorder (CKD–MBD), which shows accelerated aging due to increased vascular calcification. Additionally, Klotho acts in an endocrine manner participating in different signaling pathways as an anti-inflammatory, antioxidant, anti-fibrotic and anti-aging mediator, preserving vascular structure and function.

Principal conclusions: Klotho is a possible early marker for the detection and monitoring of subclinical arterial calcification in patients with CKD–MBD and in the general population.

KEYWORDS

α-Klotho; Vascular calcification; Chronic kidney disease–mineral bone disorder; Fibroblast growth factor 23; Hyperphosphatemia

Introduction

Endothelial cells gradually increase permeability as they become dysfunctional and support the accumulation of low-density lipoproteins, inflammatory mediators and activated leukocytes in the intima[1,2], which promotes fibroproliferative changes[3] and the incorporation of calcium in the vascular wall[4]. Medial calcification, which appears mostly in small- and medium-sized arteries, differs from intimal calcification in the atherosclerosis of large arteries, as the calcification process is tightly regulated by the type of damage to vascular smooth muscle cells[4]. Medial calcification is responsible for vessel stiffness, systolic hypertension and increased pulse wave velocity, leading to increased diastolic dysfunction and heart failure, whereas intimal calcification is associated with arterial obstruction and plaque rupture[2,5], mostly causing acute myocardial infarction or cerebrovascular insult. Both types of vascular calcification may result in life-threatening complications. Currently, according to the WHO, 17.9 million people die due to cardiovascular diseases, 85% of which are caused by heart and brain infarction[6]. Arterial wall calcification is increased in patients with metabolic syndrome, diabetes and in postmenopausal women affected by osteoporosis[4]. Vascular and soft tissue calcifications occur especially in patients with chronic kidney disease–mineral and bone disorder (CKD–MBD)[7,8,9]. International CKD–MBD incidence, prevalence, mortality and disability-adjusted life years have increased significantly since 1990 due to population expansion, aging and an increased number of patients with diabetes and hypertension, which are the leading causes of CKD–MBD[10]. Therefore, the relevance of vascular calcification assessment in CKD–MBD is widely recognized in clinical practice. Radiographic and ultrasound methods depict existing atherosclerosis when it is too late for primary prevention and early treatment[11].

The assessment of endothelial dysfunction[12] and the analysis of arterial stiffness[2,13] enable earlier diagnosis, and improve the monitoring of vascular changes in pro-inflammatory conditions and during therapy. Simultaneously, many attempts have been made to analyze the pathogenesis of vascular calcifications and to design the markers for their early detection with the aim of preventing the adverse events of cardiovascular diseases. Research data shows that Klotho plays a pivotal role in vascular calcification by orchestrating calcium/phosphate/magnesium homeostasis[14,15] besides its additional extreme pleiotropic actions[16].

Physiological distribution and function of Klotho protein

The Klotho family of proteins comprises α-, b- and g- homologous isoforms[17,18] created by the transcription of the Klotho gene with pleiotropic functions[19,20]. The most investigated isoform is α-Klotho or Klotho (unless otherwise specified). Klotho is a constitutive protein of the cell membrane[19], which is widely spread throughout the body and differently expressed in various cells[21]. Using the immunohistology method, Klotho positive staining was found in human epithelial and neural cells (pituitary and thyroid glands, pancreas, medullary cells of the adrenal gland, neurons of the myenteric plexus of the intestine, and neurons of the brain and spinal cord, including Purkinje cells and motoneurons in the gray matter and spinal cord)[22]. Klotho was found in human epithelial cells of the epidermis, hair follicle and sebaceous glands, the epithelial cells of the jejunum and colon, urinary bladder, the female and male reproductive system (testicular Sertoli and Leydig cells, prostate, mammary tissue, placenta, endometrium and salpinx) and skeletal

muscle[22,23]. Klotho is distributed in the arteries of various organs but has never been observed in the liver[22]. However, the highest expression of the Klotho gene and protein was found in mouse[24,25] and human[22,26] kidneys. A more intense labelling of Klotho in the apical side of the epithelial cells of the distal tubule and collecting tubules than in the proximal tubules in humans[22] suggests the site of its extensive action in the kidney.

Klotho appears as a component of the fibroblast growth factor 23 (FGF-23) receptor-activating complex[15,27] in sensitive kidney tubules[22] and vascular tissue[21]. The ligation of FGF-23 to the FGF receptor/Klotho complex in proximal renal tubules was found to decrease phosphate reabsorption, reduce the serum phosphate concentration and increase phosphaturia[28], thus protecting the kidneys from aging[29]. FGF-23 quenches the activity of 1α-hydroxylase and hampers the synthesis of 1α,25-dihydroxycholecalciferol in proximal kidney tubules[28]. Simultaneously, FGF-23 facilitates calcium and sodium resorption in distal kidney tubules by increasing calcium channel expression and the sodium-chloride cotransporter in epithelial cells[28]. These seemingly opposite mechanisms explain the complexity of the influence of Klotho and FGF-23 on the metabolism of vitamin D, calcium and phosphorus in animal models and in humans[27], which has been extensively investigated in the context of cardiovascular health.

The Klotho transmembrane domain can be shed from the cell surface after cleavage by metalloproteases ADAM-10 and ADAM-17[27,30]. Thus, soluble Klotho is detected in urine from healthy subjects[31], although it is unstable in such a complex medium and degrades after a few hours despite the addition of protease inhibitors or albumin[32]. Moreover, the soluble form of Klotho becomes the main functional form in circulation[33], and it is detected in the plasma of rodents and humans[34]. Klotho participates in diverse signaling pathways[23].

Soluble Klotho can become a constituent of the FGF-23/Klotho receptor complex; however, it also acts independently of FGF-23 in an endocrine manner as an anti-inflammatory, antioxidant, anti-fibrotic and anti-aging mediator, thus preserving vascular structure and function. It down-regulates nuclear factor kappa-B (NF-κB) and NF-κB-mediated translation of genes for proinflammatory cytokines in chronic and degenerative diseases, decreasing inflammation[20,35]. Klotho suppresses aldosterone action[36]. Additionally, Klotho defends human aortic cells against reactive radicals developed in oxidative stress in experimental models *in vitro*[37]. In mammals, Klotho antagonizes insulin and insulin-like growth factor-1 (IGF-1) signaling by the activation of Forkhead box O (FoxO) transcription factors and manganese superoxide dismutase, which removes reactive oxygen radicals, thus potentially decreasing aging[38]. Klotho is found in the cerebrospinal fluid[34], where it protects hippocampal neurons from oxidative damage and degeneration in mice[39] and rats[40], thus preserving cognitive and neurobehavioral functions. A cross-sectional study by Wu et al. showed that the decrease in β-Klotho was closely related to the development of depressive symptoms in patients with stable coronary artery disease[41]. A fragment of human Klotho — the human Klotho protein 1 — binds to the TGF-β receptor 2 instead of TGF-β, and inhibits the TGF-β-induced activation of Smad2/3 and mitogen-activated protein kinases involved in fibrosis, which is characteristic for tissue remodeling[42]. Klotho directly binds to endogenous Wnt ligands and prevents canonical Wnt/β-catenin signaling responsible for cardiac and renal injury in cardiorenal syndrome[43,44,45], and directly participates in phosphate and calcium regulation, preventing vascular calcifications and aging[18]. Therefore, vascular, cardio-renal and cognitive anti-aging properties are assigned to Klotho.

Pathophysiological role(s) of Klotho in vascular calcification

Calcium and phosphorus concentrations are important for the initial structural changes of smooth muscle cells in the arterial wall, which precede the process of vascular calcification in intima and media in rodents and humans[46,47]. The Klotho/FGF-23 axis has been extensively investigated in the context of calcifying conditions in hyperphosphatemia, as the Klotho protein physiologically promotes phosphate elimination mediated by FGF-23[28]. A mutated human Klotho gene generates a dysfunctional protein and impairs FGF-23 bioactivity in the regulation of phosphate and vitamin D homeostasis[48], suggesting that circulating[9] and vascular[21,22] Klotho is implicated in the process of vascular calcification. Patients with vascular calcification and developed atherosclerosis express decreased serum Klotho and an increased concentration of FGF-23, depending on the degree of calcification compared with the control[49]. These findings led to the conclusion that Klotho protein is a valuable marker for monitoring vascular calcifications, even in preclinical phases[49]. Klotho protein is found in the smooth muscle cell layers of the human aorta by staining of the intima, media and the vasa vasorum, as well as in renal, intrarenal, thyroid, prostate and testicular arteries[21,22]. The expression of Klotho in tunica media in medium-sized muscular human arteries has always been more prominent in healthy subjects than in patients with CKD–BMD[21]. In contrast to the abovementioned data, the extensive validation of Klotho, which was performed by Mencke and collaborators, using immunohistochemistry, immunofluorescence, quantitative reverse transcriptase-polymerase chain reaction and western blotting using different anti-Klotho antibodies in renal and iliac arteries of healthy human renal donors and renal graft recipients, carotid endarterectomy specimens and cultured human aortic smooth muscle cells, practically did not show Klotho expression[50]. This probably indicates a different specificity of the antibodies used towards Klotho antigens.

An initial decrease in Klotho appears in inflammatory conditions[51], comprising arterial hypertension and an unregulated metabolism of carbohydrates and lipoproteins, all of which have low-grade inflammation and oxidative stress as an underlying factor[9]. Pro-inflammatory transcription factor NF-κB ligates the Klotho promoter and inhibits Klotho protein synthesis[52], explaining depressed serum Klotho levels in inflammatory conditions characterized by an increased number of white blood cells, uric acid, or inflammatory marker C-reactive protein in humans[53]. One study reported that prominent oxidative stress and the aging of endothelial cells mediated by circulating toxins and NF-κB activation–decreased Klotho, particularly in uremia, can be restored by the addition of Klotho protein[20]. Vascular calcification is inversely correlated with vascular Klotho expression in healthy subjects[21]. In a study by Lim et al., a lack of vascular Klotho protein in humans was accompanied by a lack of receptors 1 and 3 for FGF-23 in the arterial wall, which might be responsible for disabled FGF-23 signaling in the aorta in the experimental animal model, but vascular cells are a Klotho-dependent target tissue for FGF-23[21]. FGF-23 mediates cellular activation by phosphorylation of extracellular signal-related kinases and serine/threonine-specific protein kinases, important for cellular proliferation, which were abrogated following Klotho knockdown[21]. Vascular Klotho deficiency could be restored by vitamin D supplementation in human arterial organ cultures from patients with CKD–MBD[21]. Experimental data on animal models confirmed the results of human tissue research. The substitution of Klotho in α-Klotho-deficient mice with severe vascular calcification hampers calcification[52]. It ameliorates vessel structure, kidney performance and serum phosphate levels,

suggesting a significant repercussion of α-Klotho on vascular health and longevity[7,52]. It has been recently shown that soluble Klotho directly suppresses the transport of sodium-dependent phosphate and calcification supported by phosphates in the mouse aorta[54]. Moreover, studies have demonstrated that a topical administration of α-Klotho reduced the calcification of vessels in mice[54], and α-Klotho preserved vascular smooth muscle cell differentiation *in vitro*[52].

Klotho and CKD–MBD

CKD–MBD represents a systemically impaired health status with persistent low-grade inflammation, oxidative stress, an altered metabolism of ions often associated with dysglycemia, plasma lipids and coagulation, resulting in premature aging[55]. In such altered metabolic conditions alongside a TNF-α-mediated inflammatory process[21], vascular calcification progresses rapidly[47] in the form of severe vascular medial calcification and accelerated atherosclerosis[56]. Studies conducted in patients with CKD–MBD demonstrated that accelerated calcification occurred due to a Runx2 and myocardin-serum response factor-dependent signaling, suggesting osteogenic transformation[21].

A decrease in Klotho concentrations in the urine and serum[51] is the earliest event during the deterioration of acute[7,57] and chronic kidney function[18,39,58–60], which in turn exacerbates kidney damage. The prevention of Klotho decline by several mechanisms can attenuate renal injuries, slow down CKD progression, ameliorate extrarenal complications and improve renal function[31]. A decrease in serum Klotho is considered an indicator and predictor of mortality from cardiovascular diseases not only in patients with CKD–MBD[61] but also in the general population[15,58]. A decreasing Klotho concentration negatively correlates with the increase in high-sensitivity C-reactive protein and it emerges as a non-traditional inflammation-mediated risk factor for atherosclerosis in hemodialysis patients[62]. The progression of autosomal dominant polycystic kidney disease is characterized by an increase in FGF-23 concentration and a decrease in circulating Klotho concentration[63]. Some studies revealed that these changes were associated with increased carotid artery intima–media thickness, brachial artery pulse wave velocity, creatinine concentration and 1α25(OH) cholecalciferol, and negatively correlated with eGFR[63].

Furthermore, an increase in FGF-23 due to hyperphosphatemia and a deficit of Klotho are independently combined with the development of cardiovascular comorbidities and mortality in patients with CKD–MBD[15,58]. Namely, hyperphosphatemia is an early sign of disturbed renal ion metabolism and a prerequisite for the arterial calcification process[64]. It significantly contributes to the enlargement of arterial and valvular calcifications in patients with CKD–MBD[65,66]. Hyperphosphatemia is inefficiently regulated without Klotho expression[7], as Klotho promotes FGF-23-mediated phosphate elimination[28,29,66]. A deficiency of Klotho or FGF-23 in mice with CKD–MBD leads to hypervitaminosis D, hypercalcemia and hyperphosphatemia[27], contributing to an accelerated aging phenotype[67] and soft tissue calcification[7]. In contrast, a study by Hu et al. reported that when compared with wild-type mice with CKD–MBD, transgenic mice with CKD–MBD overexpressing Klotho showed better kidney function with preserved glomerular function and enhanced phosphaturia, accompanied by diminished vascular calcification due to a direct restraint of phosphate intake in arterial smooth muscle cells[7]. A low-phosphate diet prevents soft tissue calcification although vitamin D rises, encouraging the opinion that hyperphosphatemia is more significant than vitamin D insufficiency in the process of aging[67]. It seems that Klotho

interacts with magnesium to regulate vascular function in CKD–MBD. Hypomagnesemia aggravates kidney injury by increasing kidney tubule load with phosphate, which leads to the lowering of Klotho protein in tubular epithelial cells as early as in moderate CKD–MBD[68]. Magnesium reverses arterial calcium deposits by directly impeding non-canonical Wnt signaling[68], as does Klotho[29]. Vitamin D[29] and FGF-23[58] increase α-Klotho transcription in mice. However, α-Klotho expression can vary in different arteries[21,22], and the results of experiments on animal models cannot be simply interpolated to humans.

Klotho and carotid artery stenosis

One study demonstrated that the concentration of serum Klotho correlated negatively with carotid intima–media thickness, carotid atherosclerotic plaque quantity and atherosclerosis in hemodialysis patients[62]; however, the causal association of Klotho with ischemic stroke was not found in another meta-analysis[69]. Patients on continuous ambulatory peritoneal dialysis also largely suffer from carotid artery calcification (~ 50%), which is associated with a decreased serum Klotho concentration and elevated FGF-23 in patients of approximately 70 years of age[70]. One study concluded that healthy adults[33] and patients with type 1 diabetes[71] with low serum Klotho concentrations had weaker flow-mediated dilatation, larger carotid intima–media thickness and greater epicardial fat thickness compared with the high serum Klotho group[33]. Increased circulating Klotho protects against subclinical carotid atherosclerosis in patients infected with HIV and treated with combined antiretroviral therapy, and has always been associated with lower fasting glucose[72]. In contrast, serum Klotho may be increased in patients with subclinical carotid atherosclerosis suffering from type I diabetes with normal kidney function, who do not have clinically recognized cardiovascular events[73], suggesting that atherogenesis in patients with diabetes could take place independently of serum Klotho concentration. Klotho gene polymorphisms may support atherosclerosis, and Klotho single nucleotide polymorphism is associated with intima–media thickness and carotid atherosclerosis in patients with hypertension[74]. This suggests that Klotho might protect the carotid artery against atherosclerosis[71], having in mind that secretion and plasma concentrations of Klotho decrease with age[75]. Moderate aerobic exercise increases circulating Klotho concentrations, as shown in postmenopausal women, and provides beneficial effects on carotid artery stiffness, which is the measure of vascular calcification[75]. In the mentioned study, Klotho negatively correlated with the stiffness index and positively with increased carotid artery compliance and aerobic exercise capacity measured with oxygen uptake at the ventilatory threshold[75].

Klotho and coronary artery disease

Klotho deficiency correlates with the occurrence and development of coronary artery disease, atherosclerosis, myocardial infarction and left ventricular hypertrophy[69,76]. Circulating Klotho concentrations are inversely associated with the presence and severity of coronary artery disease and in the case of ischemia-based atrial fibrillation[69,77]. However, a study conducted by Koga et al. showed that serum soluble Klotho concentrations inversely correlated with the calcium index in patients with stable coronary artery disease who were scheduled for percutaneous coronary

intervention following intravascular ultrasound[78]. A study by Keles et al. conducted in patients with type 1 diabetes showed that decreased serum Klotho concentrations followed the decrease in sensitive ultrasound indicators of the left ventricular contraction (global longitudinal strain of the left ventricle) and the increase in endothelial dysfunction (flow-mediated dilation of the brachial artery) and epicardial fat thickness, representing an early predictor of atherosclerosis[71]. Klotho gene transfer protects the coronary artery in diabetic rats, as demonstrated by the increased concentration of high-density lipoproteins and decreased coronary artery intima thickness and intima-media ratio[79]. Among patients on hemodialysis, those with low serum Klotho had higher carotid intima-media thickness, left ventricle mass, left ventricle index and left ventricle ejection fraction (LVEF) than patients with high serum Klotho, as reported by Abdallah et al[80]. In these patients, serum Klotho concentrations negatively correlated with systolic pressure and pulse pressure[62]. In a study that included patients with CKD–MBD, a decrease in circulating Klotho did not correlate with the severity of coronary artery calcifications and aortic valve calcification[9], suggesting the complex pathogenesis of coronary artery disease in patients with CKD–MBD. However, higher plasma circulating Klotho levels reduce cardiovascular risk, suggesting Klotho has a protective role in cardiovascular diseases[78,81,82].

Possible clinical application of Klotho and conclusion remarks

Klotho is considered a novel cell-protective factor in cardiovascular diseases[76]. In experimental animal models, the phenotype of a shortened lifespan, vascular calcification and cardiovascular disease with multiple organ degeneration and weakness has been attributed to the abolished expression of the Klotho gene[26]. Klotho expression decreases in diabetes[71], primary and secondary arterial hypertension[36], coronary artery disease[78], carotid stenosis[62], renal allograft biopsies during delayed graft function[23] and in plasma during acute kidney injury[16], whereas the most prominent decrease of Klotho is found in patients with CKD–MBD[18,60], causing accelerated aging[48] due to increased vascular calcification and the complexity of its actions[55]. Klotho expression at protein and mRNA levels in PBCs is a novel and valuable marker of subclinical atherosclerosis in patients with CKD–MBD[49] and in the general population[83], which predicts and monitors disease progression during therapy.

Its clinical applications for the treatment of cardiovascular diseases have lately been debated, and Klotho activity modulation seems to be an attractive target for therapeutic intervention in a select group of patients, primarily those with CKD–MBD, as Klotho is ascribed vascular and cardiorenal protective properties due to its anti-inflammatory[20], anti-oxidant[37,38], anti-fibrotic[42] and anti-aging functions[18].

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

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Ethical statement

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SAŽETAK

Vaskularna kalcifikacija regulirana Klotho proteinom tijekom fiziološkog i patofiziološkog starenja

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Svrha studije: Široko rasprostranjen membranski i topivi Klotho protein igra ključnu ulogu u vaskularnoj kalcifikaciji podešavanjem homeostaze kalcija, fosfata i magnezija posredovanog kompleksom Klotho / receptor čimbenika rasta fibroblasta 23. Cilj je bio pregledati nove znanstvene rezultate i raspraviti ulogu Klotho proteina u kalcifikaciji arterija.

Osnovni postupci bili su pregled literature o Klotho proteinu i njegovim mehanizmima djelovanja tijekom fiziološkog i patološkog starenja.

Glavni nalazi: Nedostatak Klotho proteina odražava se na skraćeni životni vijek, vaskularnu kalcifikaciju i kardiovaskularne bolesti s degeneracijom više organa i slabošću organizma u eksperimentalnim modelima životinja. Najizraženije smanjenje Klotho proteina i mRNA kod ljudi nalazi se u bolesnika s kroničnom bolešću bubrega – mineralnim i koštanim poremećajem (CKD–MBD), koji pokazuju ubrzano starenje zbog povećanih vaskularnih kalcifikacija. Klotho djeluje na endokrini način sudjelujući u različitim signalnim putovima kao protuupalni, antioksidativni i antifibrotični posrednik te protiv starenja koji čuva strukturu i funkciju arterija.

Glavni zaključci: Klotho je mogući rani marker za otkrivanje i praćenje subkliničkih arterijskih kalcifikacija u bolesnika s CKD–MBD i u općoj populaciji.

KLJUČNE RIJEČI

α-Klotho; Vaskularna kalcifikacija; Kronična bubrežna bolest – mineralni i koštani poremećaj; Čimbenik rasta fibroblasta 23; Hiperfosfatemija