AJKD

Narrative Review

Chronic Kidney Disease: A Clinical Model of Premature Aging

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Premature aging is a process associated with a progressive accumulation of deleterious changes over time, an impairment of physiologic functions, and an increase in the risk of disease and death. Regardless of genetic background, aging can be accelerated by the lifestyle choices and environmental conditions to which our genes are exposed. Chronic kidney disease is a common condition that promotes cellular senescence and premature aging through toxic alterations in the internal milieu. This occurs through several mechanisms, including DNA and mitochondria damage, increased reactive oxygen species generation, persistent inflammation, stem cell exhaustion, phosphate toxicity, decreased klotho expression, and telomere attrition. Because recent evidence suggests that both increased local signaling of growth factors (through the nutrient-sensing mammalian target of rapamycin) and decreased klotho expression are important modulators of aging, interventions that target these should be tested in this prematurely aged population.

Am J Kidney Dis. xx(x):xxx.

INDEX WORDS: Chronic kidney disease; aging; cardiovascular disease; mammalian target of rapamycin (mTOR); klotho; phosphate; inflammation; oxidative stress.

Peter Stenvinkel, MD, PhD, was an International Distinguished Medal recipient at the 2012 National Kidney Foundation Spring Clinical Meetings. The International Distinguished Medals are awarded to honor the achievement of individuals who have made significant contributions to the field of kidney disease and extended the goals of the National Kidney Foundation.

The prevalence of chronic kidney disease (CKD) has reached epidemic proportions, and today ~10% of the population shows signs of decreased kidney function.[1] Patients with CKD are at increased risk of premature death, mainly due to a high risk of cardiovascular disease and infections, which often occur in combination with protein-energy wasting.[1] Cardiovascular risk increases early in the course of CKD progression,[2] and the non-normalized cardiovascular mortality risk in European patients starting dialysis therapy is 15-fold higher than that in the general population,[3] with the relative death risk being even higher in the United States.[4] Because the uremic phenotype is characterized by many features of aging, such as osteoporosis, atherosclerosis, poor wound healing, sarcopenia, infections, inflammation, oxidative stress, insulin resistance, frailty, hypogonadism, infertility, skin athrophy, cognitive dysfunction, and disability, CKD could be seen as a premature aging (or progeroid) syndrome. Because kidneys are among the organs most sensitive to the aging process,[5] the link between aging and decreased kidney function is birectional. Yang and Fogo[6] have suggested that manipulation of cell senescence, which is an important mechanism for preventing the proliferation of potential cancer cells, may be a future way to manipulate the age-associated decrease in kidney function.

THE BIOLOGICAL PROCESS OF AGING

As a consequence of improvements in life conditions and medical care, today humans can live longer than 100 years, a considerably longer time than that of our ancestors. The longest documented human life span is that of Jeanne Calment (1875-1997), a French woman who lived long enough to both meet Vincent van Gogh and experience the internet. Research in aging is a young field and aging has turned out to be a complex process controlled by many transcription factors and signaling pathways.[7] Although aging seems to occur in most species, many animals living in the natural environment do not become senescent because they die of disease, starvation, and predation before they reach old age.[8,9] Even so, the phenomenon of negligible senescence, which is characterized by an attenuated age-related change in reproductive and physiologic functions, as well as no observable age-related gradual increase in mortality rate,[9] has been documented. Among long-lived animal species such as turtles and rougheye rockfish, the naked mole rat has attracted much interest because recent data show that this eusocial mammal lives up to 8 times longer than mice. In addition, naked mole rats are extremely

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Received August 22, 2012. Accepted in revised form November 19, 2012.

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0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2012.11.051

Box 1. Examples of Main Theories of Aging

- Evolutionary theory: based on Darwin's theory of natural selection
- Free radical theory: oxidative stress is considered a major cause of premature aging
- Mitochondrial theory: extension of the free radical theory
- Gene regulation theory: cellular senescence is the result of changes in gene expression
- Inflammation hypothesis: inflammation is considered a major part of the aging process
- Telomere theory: a limitation in replicative capacity after a certain number of cell divisions
- Immune theory: the immune system is a powerful mechanism to face stressors
- Neuroendocrine theory: aging is due to changes in endocrine and neural function
- Neuroendocrine-immuno theory: a combination of the immune and neuroendocrine theories
- Phosphate retention theory: a novel theory based on the finding that dietary restriction of phosphate attenuates the aging characteristics in klotho null mice[13]

Source: Tosato et al.[12]

resistant to neoplasia, oxidants, toxins, and oxygen deprivation.[10] Lewis et al[11] recently demonstrated that enhanced cell signaling through the tumor suppressor protein p53 and the transcription factor Nrf2 protects cells in naked mole rats, suggesting that further studies of the role of these proteins in the aging process are warranted. Improved understanding of the processes that have evolved in these specific species to increase healthy life spans provides unique opportunities to develop novel treatment strategies against human aging.

Aging commonly is defined as the progressive accumulation of deleterious changes in cells and tissues that are responsible for deterioration in physiologic functions coupled with increased vulnerability and risk of death. Tosato et al[12] discussed several different hypotheses of aging (summarized in Box 1). The permanent and irreversible growth arrest of cell senescence is a central paradigm of aging. Although senescent cells remain viable, they are unable to divide and their morphologic characteristics change and undergo significant transcriptional changes accompanied by delayed repair, as well as alterations in nuclear structure, gene expression, protein processing, and levels of growth factors (Fig 1). Recent evidence suggests that the mammalian target of rapamycin (mTOR) is involved in the hypersecretory senescent phenotype.[15] Among tumor suppressor proteins that are crucial in the induction of senescence, p53 (the "guardian of the genome") has an especially important role in protecting against DNA damage, oxidative stress, and telomere attrition. Cellular senescence may occur prematurely in response to a variety of stress factors, such as oxidative stress, DNA damage, and inflammation.[16] Notably, decreased kidney function per se and the uremic mileu affect most of the factors known to accelerate aging, including DNA damage, inflammation, phosphate toxicity, klotho deficiency, oxidative stress, exhaustion of stem cells, and telomere shortening.[17]

THE ANTAGONISTIC PLEIOTROPHY HYPOTHESIS

Of the multiple theories to explain exceptional longevity, the most robust has centered on the decreased signaling of anabolic hormones: growth hormone (GH), insulin-like growth factor (IGF), and insulin. Despite ample evidence in the literature that deficiencies in GH and IGF-1 contribute to several aspects of the natural aging process, animal studies show that disrupting the signaling pathways for these hormones exerts antiaging effects.[18] Potential mechanisms linking decreased signaling of these hormones with delayed aging include increased hepatic sensitivity to insulin actions, decreased plasma glucose levels, increased resistance to oxidative stress, and decreased mTOR signaling.[18] Thus, familial longevity usually is associated with better insulin sensitivity.[19] At least 7 genetic mouse models (including mice null for either GH receptor/binding protein or mice heterozygous for the IGF-1 receptor) have been reported to show increased life span and a delay in aging-related diseases.[20] Sonntag et al,[21] who recently summarized the literature on GH and IGF-1 and aging processes, suggested that the perceived contradictory roles of these anabolic hormones are explained by their differential effects on health during specific life span stages. In this context, the antagonistic pleiotrophy hypothesis[22] should be mentioned; this hypothesis posits that gene products have opposite effects on biological fitness at different stages of life. Based on this hypothesis, Blagosklonny[23] suggested that although mTOR activation by IGF-1, GH, insulin, and nutrients may provide a selective survival advantage to young males (because it stimulates muscle growth and increases competitive and reproductive ability), mTOR overactivation may accelerate age-related diseases (Fig 2). It recently was shown that increased mTOR signaling in hypothalamic neurons that express pro-opiomelanocortin contribute to age-dependent obesity.[24] Moreover, interventions that inhibit mTOR, such as rapamycin and caloric restriction, lead to changes in gene expression and to increased life span in both animals[25] and humans.[26] Thus, because single-gene mutations in those genes involved in insulin/IGF and mTOR signaling pathways extend life span,[27] dampening the mTOR pathway may protect from age-related diseases.

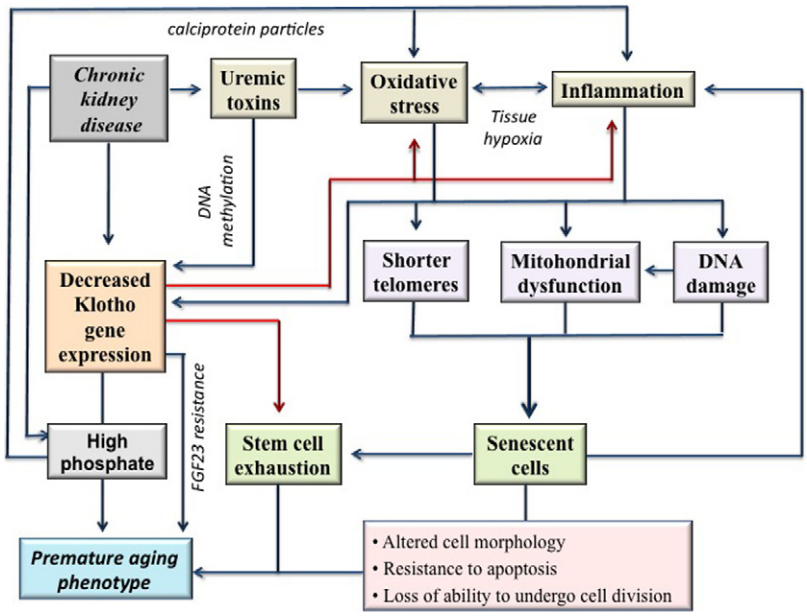

Figure 1. The putative progeroid effects of the uremic mileu in which phosphate retention, decreased klotho expression, and accumulation of uremic toxins promote oxidative stress and inflammation, which through telomere attrition and DNA and mitochondrial damage may cause cellular senescence and stem cell exhaustion, factors that in turn may promote vascular disease and premature aging. It could be speculated that retaining phosphate may further promote inflammation through the formation of calciprotein particles. It should be noted that other factors that may affect the aging process, such as changes in body composition, comorbid conditions, hormonal changes, and vitamin D deficiency, are not included in this figure. Also, sodium storage may induce a macrophage-driven response that also predisposes to inflammation.[14] Abbreviation: FGF23, fibroblast growth factor 23.

Pregnancy-associated plasma protein A (PAPP-A) was identified first in high concentrations in pregnant women in 1974 and its function was unknown for 25 years. Today we have learned that this protein is stimulated by proinflammatory cytokines and has a role in the progression of atherosclerotic plaque development through enhanced local IGF-1 bioavailability.[28] Mice null for PAPP-A are resistant to the development of atherosclerosis[29] and live ~30% longer than their wild-type littermates.[30] Because elevated PAPP-A levels have been found in patients with CKD stage 4,[31] the role of this protein in premature uremic vascular aging needs further study.

PERSISTENT INFLAMMATION AND CELLULAR SENESCENCE

Because most chronic diseases are associated with inflammation, it can be hypothesized that an increased inflammatory load increases the risk of age-related pathologic states and decreases survival. Elderly individuals often exhibit chronic inflammation, which is characterized by immune system dysregulation and increased inflammatory cytokine production.[32] The Newcastle 85+ Study recently confirmed the importance of inflammatory markers in frailty of the very old.[33] As discussed by Brod,[34] unregulated inflammation shortens human functional longevity and has an important role in the cause, progression, and shortened life span of patients with autoimmine diseases, presenile dementia, osteoporosis, diabetes, and atherosclerosis.

The growing importance of inflammation as a cause of aging is exemplified by the neologism "inflammaaging."[35] The consequences of inflammation also provide additional support for the antagonistic pleiotropy hypothesis in that its beneficial effects, which early in life work to neutralize dangerous and harmful agents, may become harmful themselves at an older age.[35] Of

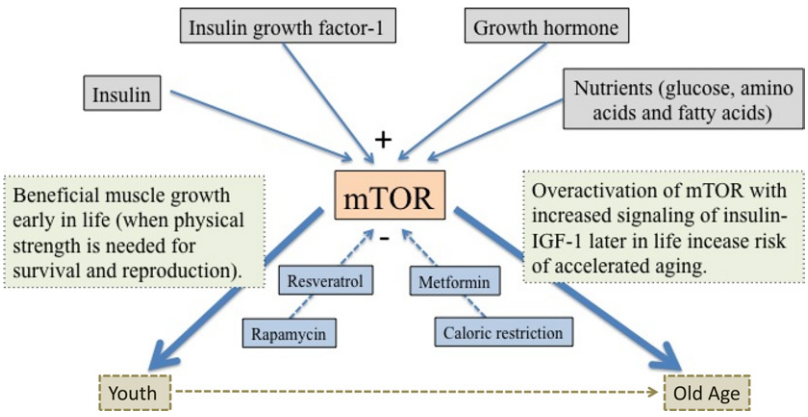

Figure 2. The activity of nutrient sensitive mammalian target of rapamycin (mTOR) regulates growth, proliferation, motility and survival in the cell as well as protein synthesis and transcription. This system is activated by growth factors and nutrients and inhibited by rapamycin, metformin, resveratrol, and caloric restriction (ie, interventions that have been shown to increase life span in animal models). Based on the antagonistic pleiotrophy hypothesis Blagosklonny[23] hypothesized that the activation of mTOR may from an evolutionary perspective be of benefit for the young male (when muscle growth for survival and reproduction is important) whereas overactivation later in life rather increase the risk of age-associated diseases and premature death. Abbreviation: IGF-1, insulin growth factor 1.

potential relevance is the observation that as human immunodeficiency virus (HIV)-infected patients live longer (due to successful treatment with antiretroviral therapy), this patient group develops premature susceptibility to the age-related morbidities and adaptive changes in the immune system ("immune-senescence") seen in older adults.[36] It has been suggested that cytomegalovirus contributes to the development of premature aging and immunosenescence in HIV-infected patients.[37]

In terms of kidney disease, because increased levels of the proinflammatory cytokine interleukin 6 (IL-6) are a common feature of uremia,[38] it is of interest that this cytokine regulates oncogene-induced senescence.[39] Because senescent cells secrete multiple growth factors, proinflammatory cytokines, and chemokines,[40] they promote further inflammation (Fig 1). Acosta et al[41] showed that senescent cells trigger a feedback loop that reinforces growth arrest through a secretory network acting through CXCR2-binding chemokines. This links cellular senescence with endothelial dysfunction and the inflammatory process of atherosclerosis.[42]

The fact that cellular senescence impairs the sucessful reprogramming of pluripotent stem cells[43] may explain why marrow-derived stromal cells[44] and endothelial progenitor cells[45] diminish in uremia. Endothelial progenitor cells and proinflammatory and proatherogenic $CD14^{++}CD16^{+}$ monocytes,[46] which are highly expressed in uremia,[47] differentiate from the same $CD34^{+}$ progenitor cells.[48] Girndt and Seibert[49] suggested that in the inflamed uremic milieu, stem cells differentiate to aggressive monocytes at the expense of reduced production of endothelial repair cells. Depleted levels of $CD34^{+}$[50] and $CD14^{+}$[51] endothelial progenitor cells are associated with decreased kidney function in patients with coronary artery disease. Thus, because the expression of nonclassical $CD14^{+}CD16^{+}$ monocytes increases with age,[52] endothelial injury,[53] and telomere attrition,[46] senescent monocytes are linked to cardiovascular disease, aging, and CKD. Another cause of accelerated senescence in human endothelial progenitor cells is carbamylated low-density lipoproteins,[54] a group of modified proteins known to have increased levels in the inflamed and oxidated uremic milieu. Because nocturnal hemodialysis was reported to be associated with the restoration of abnormal endothelial progenitor cell biology,[55] further studies are needed to determine the effect of dialysis treatment per se on the aging process. Finally, because vitamin K–dependent proteins are essential for progenitor cell proliferation,[56] additional investigations should explore whether vitamin K depletion[57] and/or warfarin treatment contribute to stem cell exhaustion in patients with CKD.

TELOMERE LENGTH AND AGING

Shortening (or attrition) of telomeres reflects not only cellular senescence, but also stem cell exhaustion, cellular hyperactivation, and a hypersecretory phenotype. Telomere length and integrity are important for optimal chromosome function and genomic integrity, and as telomeres within cells become shorter, they assume a more unstable phenotype that triggers senescence.[58] Telomeres are synthesized by the telomerases that maintain chromosome length. In certain rare forms of progeria, such as Hutchinson-Gilford progeria syndrome, premature cellular senescence results from progerin-induced telomere dysfunction.[59]

In the general population, accelerated telomere attrition is associated with cardiovascular risk factors, such as age, male sex, obesity, smoking, dyslipidemia, sedentary lifestyle, and mental stress.[60] Moreover, Shiels et al[61] showed that shorter telomeres were associated with lower socioeconomic status, inflammation, and poor diet. Because cells of the immune system are under enormous proliferative demand and stress telomere function, telomere dynamics is critical for preventing immunosenescence.[62] Infectious diseases such as cytomegalovirus[63] cause telomere attrition,[64] and telomere length correlates with both IL-6 level[65] and the cumulative inflammatory load.[66] Oxidative stress[67] and visceral fat accumulation[68] also are linked to accelerated aging and shorter telomeres. Because telomere shortening in the general population is associated with increased risk of premature myocardial infarction,[69] coronary heart disease,[69] and death,[70] telomere length is a useful aging biomarker.

Given the possibility to prevent telomere attrition by various nutritional and pharmacologic interventions, nephrologists should pay more attention to this fascinating "biological clock."[71] Ramírez et al[72] demonstrated that mononuclear cells from hemodialysis patients have decreased telomere length compared with controls and that the percentage of cells with short telomeres correlates positively with C-reactive protein level. We also have shown a correlation between telomere attrition and inflammation (as indicated by IL-6 level).[73] In our study of hemodialysis patients, decreased telomere length was associated with increased all-cause mortality independent of age, sex, and IL-6 levels.[73] Finally, Westhoff et al[74] showed that in telomerase-deficient mice, critical telomere attrition in the kidneys spurs greater apoptosis and senescence, which in turn diminishes postinjury regenerative capacity.

OXIDATIVE STRESS AND DNA DAMAGE AS PROMOTERS OF AGING

Mutations and DNA damage that lead to dysfunctional proteins and modified DNA structure have been considered a main cause of aging since the late 1950s.[75] Werner syndrome and Hutchinson-Gilford progeria syndrome are rare progeroid syndromes that clinically resemble accelerated aging. Because these diseases are characterized by defects in DNA repair and processing, this implies that increased DNA damage accelerates a decrease in physiologic processes and the development of the aged phenotype.[76] A causal contribution between DNA damage and aging was demonstrated by Niedernhofer et al,[77] who showed that when cytotoxic DNA damage is unrepaired, it triggers a highly conserved metabolic response involving the IGF-1/insulin pathway that redirects resources from growth to life extension.

The free radical and mitochondria theory of aging, which suggests that the aging process involves the initiation of free radical reactions, may explain why females live longer than males. Mitochondrial oxidative stress is higher in males and higher levels of estrogens protect females by upregulating the expression of antioxidant longevity-related genes through NF-κB (nuclear factor κB).[78] Because decreased mitochondrial function is an important factor in aging and increases the incidence of age-related disorders,[79] mitochondrial dysfunction may contribute to the growing burden of CKD in the aging population.[80] Because increased oxidative stress of DNA is a feature of uremia[81] and seems to be related to many features of the aged phenotype, including atherosclerosis,[82] a defective response to cellular DNA damage may accumulate over time and contribute to premature aging. Mutations in genomic stability genes, such as FAN1 (a DNA repair nuclease), recently were reported to connect a DNA damage response to progressive loss of kidney function.[83]

DYSREGULATION OF THE KLOTHO–FGF-23 AXIS, PHOSPHATE TOXICITY, AND AGING

The discovery of the progeric phenotype of mice that lack a functional variant of a protein that subsequently was named klotho[84] has evoked much interest among nephrologists because this "elixir of youth"[85] is highly expressed in the kidney.[84] Klotho has a short membrane-spanning domain and two large extracellular domains[86]; it exists as a transmembrane protein but also has two circulating isoforms, one of which is a shedded variant of the membrane form. Diminished tissue expression is a cardinal feature of CKD and is observed at the very earliest stages of the disease.[87] Thus, klotho has been proposed as a relevant biomarker for risk exposure associated with kidney failure. Currently, the cause of suppressed klotho levels in CKD is unknown. However, downregulation of klotho gene expression by uremic toxins and subsequent gene hypermethylation may be one plausible mechanism,[88] which implies that epigenetic dysregulation may cause some of the physiologic changes associated with aging.[89] Moreover, the fact that inflammation downregulates klotho expression through NF-κB[90] confirms the observed relationship between inflammation and accelerated organ aging.

Although a lack of klotho is associated with an aging-like phenotype, the underlying mechanisms are largely elusive. Importantly, to date there is no bioassay available for adequate detection of circulating klotho level because the recently reported assay yields substantially higher serum and urine levels than anticipated compared with immunoprecipitation techniques.[87,91] Another question is whether a decreased klotho level in tissue (predominantly the kidneys) promotes aging through direct/local mechanisms or systemic effects of klotho deficiency. Several observations support the latter theory, namely that decreased systemic klotho level is critical for accelerated aging beyond the protein's direct effects in mineral metabolism.[92,93] In this regard, in vitro studies provide evidence that soluble klotho functions as a hormone per se and directly counteracts senescence through several alternate mechanisms. Systemic delivery of recombinant wild-type klotho can ameliorate the aging phenotype in klotho mutant mice.[94] Possible mechanisms include protection against oxidative stress by activating the transcription factor FOXO and increasing the expression of superoxide dismutase downstream,[95] endogenous anti-inflammatory effects,[96] inhibition of endothelial cell senescence,[97] antifibrotic properties,[98] and prevention of vascular calcification.[87] Because suppressing the insulin/IGF-1 signaling pathway seems to have an evolutionary role for extending life,[23] the ability to suppress insulin/IGF-1 signaling also may account for klotho's antiaging properties.[99]

An alternate explanation for the link between klotho and antiaging may be its role in systemic regulation of mineral metabolism.[100] Klotho promotes renal calcium absorption and renal phosphate excretion[92,93] in addition to functioning as a permissive coreceptor for the phosphate and vitamin D–regulating hormone fibroblast growth factor 23 (FGF-23).[101] Importantly, the aging characteristics of klotho null mice are attenuated by dietary restrictions of phosphate and 1,25-dihydroxyvitamin D or by the elimination of vitamin D toxicity through ablation of the vitamin D receptor or the enzyme responsible for its activation (CYP27B1).[102-104] Collectively, the aging phenotype

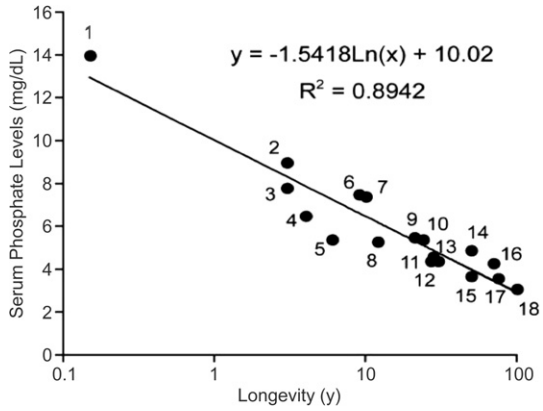

Figure 3. Association between longevity in different mammals and their systemic phosphate levels (average or median values). This strong association provides indirect support for the hypothesis that phosphate toxicity has a role in the aging mechanism. 1: Klotho knockout mouse, 2: wild-type mouse, 3: rat, 4: hamster, 5: gerbil, 6: nutria, 7: rabbit, 8: guinea pig, 9: sheep, 10: squirrel, 11: porcupine, 12: naked mole rat, 13: flying fox, 14: bear, 15: rhinoceros, 16: elephant, 17: human, and 18: human (centenarian). Adapted from Kuro-o[13] with the permission of Elsevier.

associated with klotho deficiency therefore may be due to both the intrinsic antiaging properties of klotho and secondary systemic alterations in mineral metabolism.

The finding that klotho and FGF-23 function in a common signal transduction pathway was derived from the observation that FGF-23 and klotho-deficient mice developed similar aged phenotypes, including growth arrest, nephrocalcinosis, hyperphosphatemia, hypervitaminosis D, osteopenia, hypercalcemia, emphysema, gonad atrophy, and vascular calcification.[84,101] The discovery of the klotho–FGF-23 endocrine system is important not only because it has added new dimensions to the classic view of the endocrine regulation of phosphate, but also because it indirectly linked phosphate to vascular aging. Hyperphosphatemia has been identified as a significant cardiovascular risk and mortality predictor not only in dialysis patients[105] and patients with myocardial infarction,[106] but also in individuals without CKD.[107] Moreover, hyperphosphatemia has been determined to be a cardiovascular risk factor for left ventricular hypertrophy in community-dwelling young adults.[108] Ohnishi and Razzaque[103] found that phosphate toxicity accelerates the mammalian aging process. Moreover, there is a strong inverse correlation between longevity and serum phosphate levels in different animals (Fig 3), which further supports this hypothesis.[13] Experimental studies show that phosphate promotes both vascular calcification (by increasing the genetic transcription of proteins that are involved in osteoblast function–bone formation and stimulation of matrix mineralization[109]) and apoptosis of vascular smooth muscle cells.[110] Because maintaining normal phosphate concentrations seems to be fundamental for a healthy long life, it seems logical that evolution has created many backup systems (ie, phosphatonins, such as FGF-23, FGF-7, and MEPE) aside from parathyroid hormone that protect the organism from phosphate toxicity.[111]

If the number of functional nephrons decreases to a level that fails to excrete ingested phosphate, vascular calcification and decreased life span follow. Because klotho deficiency induces FGF-23 resistance,[100] which leads to exceptionally elevated FGF-23 levels in end-stage renal disease,[112] it has been proposed that FGF-23 itself could modify the vascular phenotype. This is supported by epidemiologic data linking FGF-23 to high mortality, vascular dysfunction, and left ventricular hypertrophy across all strata of kidney function.[113,114] Also, experimental evidence suggests that FGF-23 may cause cardiac hypertrophy[115] and modulate vascular calcification.[116]

CAN INTERVENTIONS DELAY AGING?

Since the Spanish explorer Juan Ponce de Leon (1474-1521) searched for the fountain of youth in the mythical land of Bimini, humans have dreamed of preventing aging with medicines or diets. Although no such remedy works yet in humans, animal studies have shown that life expectancy can be modified.[12] Box 2 lists examples of nutritional, lifestyle, and pharmacologic interventions that have been suggested

Box 2. Examples of Interventions That May Affect Aging Processes

Nutritional and lifestyle interventions
- Caloric restriction[137]
- Red wine[117]
- Fish oil (omega-3 fatty acids)[157]
- Phosphate restriction[118]
- Physical exercise[155]

Pharmacologic interventions
- SIRT activation: resveratrol[146]
- Increased klotho expression: drugs that alter DNA hypermethylation,[119] inhibition of NF-κB,[90] PPAR-γ agonists,[120] thyroid hormones,[121] ACE inhibition,[122] vitamin D[123]
- mTOR inhibition: rapamycin,[164] metformin,[165] resveratrol[147]
- Stabilization of telomeres: statins,[124] estrogens,[125] telomerase reactivation,[126] vitamin D[127]
- Limitation of DNA damage: inhibition of NF-κB,[128] antioxidants[129]
- Phosphate lowering: phosphate binders,[130] blocking the intestinal phosphate transporter Npt2b[131]

Abbreviations: ACE, angiotensin-converting enzyme; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; PPAR, peroxisome proliferator-activated receptor; SIRT, sirtuins.

as having the potential to affect aging processes through different mechanisms. It generally is believed that the best predictor of longevity are the genes we are born with. However, Hjelmborg et al[132] uncovered scant evidence supporting the idea that genetics affects the age of death for individuals younger than 60 years, whereas in adults 60 years and older, the authors found genetics to have a moderate influence that increased over time. Nevertheless, it has been demonstrated that genes for insulin/IGF-1 signaling and telomere maintenance pathways are relevant for human longevity.[133] Centenarians have gene variants that optimally tune levels of pro- and anti-inflammatory molecules and reduce the effects of a lifetime's worth of environmental insults and stressors.[134] Moreover, functional gene variants of klotho[135] and apolipoprotein E[136] are associated with longevity.

Among the interventions that may affect life expectancy, the effects of caloric restriction (typically by 20%-40% of ad libitum consumption) while maintaining essential nutrient requirements have been studied the most, given that this intervention consistently increases the life span of mice.[137] Studies in primate species show conflicting results: Colman et al[138] reported improved survival and delayed disease onset with caloric restriction, whereas Mattison et al[139] recently reported that a caloric restriction regimen did not improve survival outcomes in young and older rhesus monkeys**.** Because of the ethical and logistical limitations of the research design and the length of a human life span, it is difficult to design studies that answer whether caloric restriction prolongs life in humans. Whereas caloric restriction reduces oxidative stress, improves cardiometabolic risk profile,[140] and deactivates the mTOR pathway,[141] it does not affect telomere dynamics in rhesus monkeys.[142] Indirect support for a benefit of caloric restriction on life expectancy is provided by studies of the Okinawan population in Japan, in whom the prevalence of centenarians is highest in the world and caloric intake is 20% lower than in the rest of Japan and 40% lower than in the United States.[12] Interestingly, higher glucose levels are associated with an older perceived age in nondiabetic patients and diabetic individuals.[143] While religious fasts are mainly undertaken for spiritual purposes, they have the potential to downregulate mTOR and affect physical health. Because caloric restriction suppresses both apoptosis in aged rat kidneys[144] and the accumulation of long-chain glycosphingolipids, which have a role in mammalian aging,[145] there is a rationale for caloric restriction in obese patients in the earlier stages of CKD. However, in later stages of CKD, when the risk of protein-energy wasting increases, caloric restriction is not advocated.

Because the beneficial effects of caloric restriction during aging may be mediated through sirtuins (SIRT1-SIRT7), the SIRT1 activator resveratrol, which accounts for the beneficial cardiovascular effects of red wine, has attracted much recent interest because this polyphenol activates both PPAR (peroxisome proliferator-activated receptor) and endothelial nitric oxide synthase and inhibits cyclooxygenase.[146] It also has been reported that resveratrol has anti-inflammatory and antioxidative effects mediated through both mTOR inhibition[147] and stimulation of the antioxidant-activated transcription factor Nrf2.[148] Accumulating in vivo evidence from disease and stress models suggests that resveratrol has a protective role and promotes human health.[146]

Red wine polyphenols also may preserve endothelial function during aging.[149] Huang et al[117] showed in a randomized trial that consuming red wine increased the number and functional capacity of circulating endothelial progenitor cells. Long-term moderate red wine consumption and equivalent oral pharmacologic doses of resveratrol increased telomere length, decreased p53 expression, and preserved vascular function indexes in normal rats; however, life span was not extended.[150] Because decreased mitochondrial oxidative phosphorylation and aerobic capacity are associated with decreased longevity, it is interesting that resveratrol treatment in mice was associated with an induction of genes for oxidative phosphorylation and mitochondrial biogenesis,[151] which suggests that resveratrol could have endurance-enhancing activities. Because resveratrol prevented wasting after mechanical unloading in rats[152] and muscle wasting in diabetic rats,[153] sirtuin activation may be a novel treatment strategy to prevent protein-energy wasting and interrupt the urea cycle in CKD.[154] The benefits of physical activity in preventing premature death have been established by many epidemiologic studies,[155] effects that may be mediated by both improved cardiometabolic risk-factor profile and effects on telomere dynamics.[156]

Upregulating telomerase pharmacologically has been proposed as a way to slow the aging process in some diseases.[126] However, these treatments inspire substantial concern about their possible carcinogenic effects. Interestingly, it has been suggested that the antiaging effects of statins are linked to their ability to inhibit telomere shortening.[124] Also, estrogen therapy[125] and higher vitamin D levels[127] seem to be associated with longer telomeres. Although marine omega-3 fatty acids are associated with telomere aging in patients with coronary heart disease,[157] there currently are not enough data to draw firm conclusions about how omega-3 fatty acids affect the aging metabolism.[158] Because NF-κB inhibition delays DNA damage–

induced senesence and aging in mice,[128] there also is a rationale for testing antioxidative[129] anti-inflammatory[159] treatment strategies to delay uremic telomere attrition.

An interesting and novel concept to extend life span is the "gerosuppressant" drug rapamycin, which reduces insulin/IGF-1 signaling by inhibiting the mTOR pathway.[160] Rapamycin has been regarded as a "double whammy"; that is, a drug that both increases life span and inhibits cancer in animal models.[161] Because of the salutory effects of rapamycin on life span in animal models, its rejuvinating effects on stem cells,[162] and the finding that Tor complex 1 controls telomere length,[163] rapamycin has the potential to be used an antiaging drug in progeroid syndromes.[164] However, given the magnitude of rapamycin-associated adverse effects, as well as the lack of human data, caution is advised regarding the routine use of rapamycin as an antiaging agent. Weaker mTOR inhibitors such as the antidiabetic drug metformin[165] and reservatrol[147] may be of more interest in this regard.

Given the role of klotho deficiency in premature aging, much interest has focused on interventions that increase systemic klotho expression.[94] Because vitamin D receptor activators are the most potent klotho expression stimulators,[166] it is possible that the survivial benefit associated with vitamin D therapy in patients with CKD may be attributed in part to an increase in klotho levels. Furthermore, the recent finding that the uremic toxins indoxyl sulfate and *p*-cresyl sulfate silence the klotho gene through hypermethylation[88] opens a new possibility of reversing the aging process by manipulating the epigenome. PPAR-γ, which suppresses NF-κB and decreases the production of cytokines and chemokines, upregulates tissue klotho and presumably also its circulatory level,[120] which implies that PPAR-γ agonists affect the aging process. Other interesting possibilities to increase klotho expression include thyroid hormones[12] and angiotensin-converting enzyme inhibitors.[122] Because a recent study implies crosstalk between FGF-23–klotho and the renin-angiotensin-aldosterone system,[167] there is an opportunity for combined treatment regimens to improve survival.

Because acute postprandial hyperphosphatemia acutely impairs endothelial function,[168] phosphate-lowering therapies may decrease cardiovascular risk and aging. Reducing phosphate levels in different animal models through means such as vitamin D receptor knockout, sodium/phosphate cotransporter knockout, low-phosphate diet, and low–vitamin D diet consistently rescue the premature aging phenotype of klotho and FGF-23 knockout mice. Thus, it has been suggested that phosphate per se may promote the aging process. Although the mechanisms by which phosphate promotes aging have not been elucidated, it can be speculated that increased oxidative stress, reduced mitochondrial respiration, and apoptosis contribute.[169] Moreover, because phosphate is associated with both C-reactive protein and fetuin A–containing calciprotein particles (stable colloidal complexes with minerals that reflect a procalcified milieu) in CKD,[170] it can be hypothesized that phosphate may promote aging through inflammatory pathways (Fig 1). No randomized controlled trial has yet proved that phosphate binders decrease mortality in dialysis patients. A recent randomized placebo-controlled pilot clinical trial in patients with moderate CKD showed that although phosphate binders significantly decrease phosphate levels and attenuate the progression of secondary hyperparathyroidism, they also promote the progression of vascular calcification.[171] These findings may be explained by increased intestinal availability and systemic absorption of free calcium when the amount of intestinal phosphate and its complex binding to calcium is decreased. Alternate strategies to reduce phosphate burden without increasing calcium absorption are desirable. Because hyperphosphatemia affects the progression of aging in both klotho mutant mice[118] and *Drosophila*,[172] dietary phosphate restriction may be a novel nutritional intervention that affects the aging process. However, dietary phosphate restriction in patients with CKD provides a greater risk of protein-energy wasting and should be monitored carefully. Another promising strategy to decrease phosphate toxicity is pharmaceutical blocking of the intestinal phosphate transporter Npt2b.[131]

CONCLUSIONS

Recent data in the gerontology literature have shed new light on the complicated process of human aging. It is noteworthy that all the proposed mechanisms of premature aging and cellular senescence, such as DNA and mitochondrial instability, inflammation, free radical excess, telomere shortening, phosphate toxicity, and systemic klotho deficiency, seem to be affected in the uremic milieu. Thus, uremia could be considered a progeroid syndrome and a clinical model to study the aging process. Because the recent literature suggests that growth factor signaling has a pivotal role in the aging phenotype, interventions targeting the nutrient-sensing mTOR pathway, such as rapamycin and resveratrol, are of major interest in studies of uremic premature aging. Given the combined role of phosphate and klotho in uremic vascular disease, interventions that target these factors also should be studied. Gerontologists and nephrologists should collaborate to further elucidate the intriguing mecha-

nisms by which decreased kidney function contributes to cellular senescence and a premature aging phenotype.

ACKNOWLEDGEMENTS

Support: The Swedish Medical Research Council and Swedish Foundation for Strategic Research supported the research of the authors.

Financial Disclosure: Dr Stenvinkel is a member of the scientific advisory board of Gambro. Since this review was written, Dr Larsson has become a part-time employee of Astellas.

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