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

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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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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.

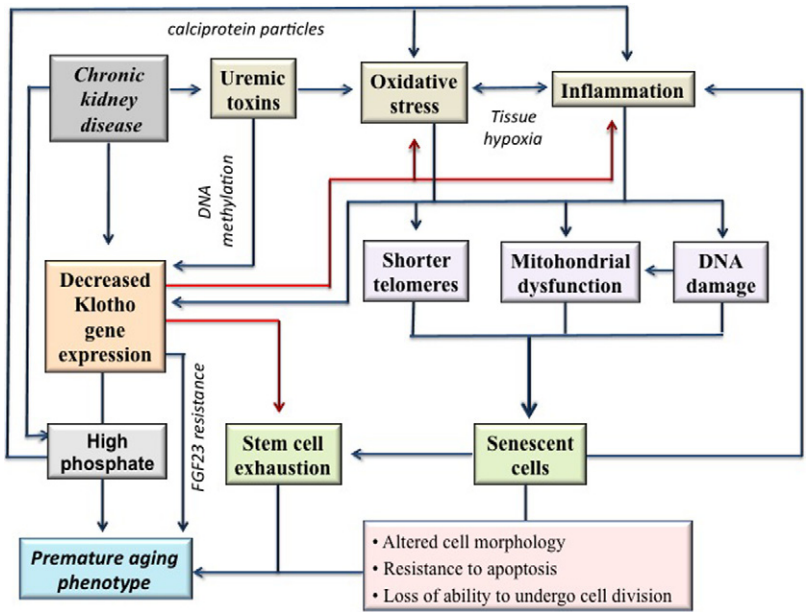

Figure 1. The putative progeroid effects of the uremic mileu in which phosphate retention, decreased klotho expression, and accumulation of uremic toxins promote oxidative stress and inflammation, which through telomere attrition and DNA and mitochondrial damage may cause cellular senescence and stem 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

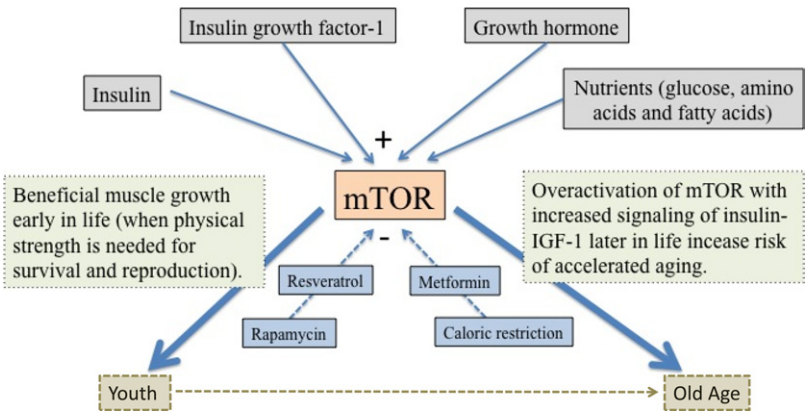

Figure 2. The activity of nutrient sensitive mammalian target of rapamycin (mTOR) regulates growth, proliferation, motility and survival in the cell as well as protein synthesis and transcription. This system is activated by growth factors and nutrients and inhibited by rapamycin, metformin, resveratrol, 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

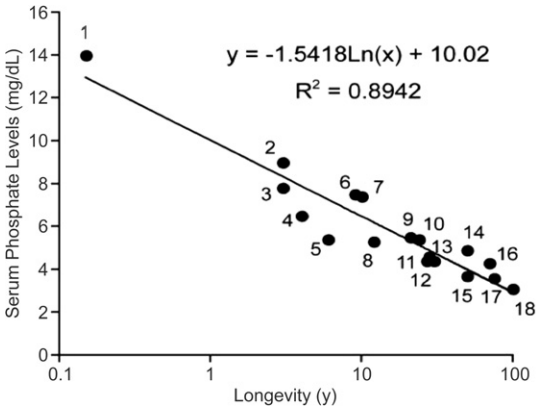

Figure 3. Association between longevity in different mammals and their systemic phosphate levels (average or median values). This strong association provides indirect support for the hypothesis that phosphate toxicity has a role in the aging mechanism. 1: Klotho knockout mouse, 2: wild-type mouse, 3: 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.

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REFERENCES

1. Stenvinkel P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. *J Intern Med*. 2010;268:456-467.

2. Vanholder R, Massy Z, Argiles A, Spasovski G, Verbeke F, Lamiere N. Chronic kidney disease as cause of cardiovascular morbidity and mortality. *Nephrol Dial Transplant*. 2005;20:1048-1056.

3. de Jager DJ, Grootendorst DC, Jager KJ, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA*. 2009;302:1782-1789.

4. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal failure. *Am J Kidney Dis*. 1998;32(suppl 5):S112-S119.

5. Kanasaki K, Kitada M, Koya D. Pathophysiology of the aging kidney and therapeutic interventions. *Hypertens Res*. 2012; 35(12):1121-1128.

6. Yang H, Fogo AB. Cell senescence in the aging kidney. *J Am Soc Nephrol*. 2010;21:1436-1439.

7. Wiggins J. Why do our kidneys get old? *Nephron Exp Nephrol*. 2011;119(suppl 1):e1-e5.

8. Finch CE. Update on slow aging and negligible senescence—a mini review. *Gerontology*. 2009;55:307-311.

9. Buffenstein R. Negligible senescence in the longest living rodent, the naked mole-rat: insights from a successfully aging species. *J Comp Physiol [B]*. 2008;4:439-445.

10. Kim EB, Fang X, Fushan AA, et al. Genome sequencing reveals insights into physiology and longevity of the naked mole rat. *Nature*. 2011;479:223-227.

11. Lewis KN, Mele J, Hornsby PJ, Buffenstein R. Stress resistance in the naked mole-rat: the bare essentials—a mini-review. *Gerontology*. 2012;58:453-462.

12. Tosato M, Zamboni V, Ferrini A, Cesari M. The aging process and potential interventions to extend life expectancy. *Clin Interv Aging*. 2007;2:401-412.

13. Kuro-o M. A potential link between phosphate and aging—lessons from klotho-deficient mice. *Mech Ageing Dev*. 2010;131: 270-275.

14. Machnik A, Neuhofer W, Jantsch J, et al. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. *Nat Med*. 2009;15:545-552.

15. Narita M, Young AR, Arakawa S, et al. Spatial coupling of mTOR and autophagy augments secretory phenotypes. *Science*. 2011;332:966-970.

16. Ben-Porath I, Weinberg RA. The signals and pathways activating cellular senescence. *Int J Biochem Cell Biol*. 2005;37: 961-976.

17. Blagosklonny MV, Campisi J, Sinclair DA, et al. Impact papers on aging in 2009. *Aging*. 2010;2:111-121.

18. Bartke A. Growth hormone, insulin and aging: the benefits of endocrine defects. *Exp Gerontol*. 2011;46:108-111.

19. Wijsman CA, Rozing MP, Streefland TC, et al. Familial longevity is marked by enhanced insulin sensitivity. *Aging Cell*. 2011;10:114-121.

20. Liang H, Masoro EJ, Nelson JF, Strong R, McMahan CA, Rickardson A. Genetic mouse models of extended lifespan. *Exp Gerontol*. 2003;38:1353-1364.

21. Sonntag WE, Csiszar A, deCabo R, Ferrucci L, Ungvari Z. Diverse roles of growth hormone and insulin-like growth factor-1 in mammalian aging: progress and controversies. *J Gerontol A Biol Sci Med Sci*. 2012;67:587-598.

22. Williams GC. Pleiotrophy, natural selection and the evolution of senescence. *Evolution*. 1957;11:398-411.

23. Blagosklonny MV. Why men age faster but reproduce longer than women: mTOR and evolutionary perspectives. *Aging (Albany NY)*. 2010;2:265-273.

24. Yang SB, Tien AC, Boddupalli G, Xu AW, Jan YN, Jan LY. Rapamycin ameliorates age-dependent obesity associated with increased mTOR signaling in hypothalamic POMC neurons. *Neuron*. 2012;75:425-436.

25. Partridge L, Alic N, Bjedov I, Piper MD. Aging in *Drosophila*: the role of the insulin/IGF and TOR signalling network. *Exp Gerontol*. 2011;46:376-381.

26. Harries LW, Fellows AD, Pilling LC, et al. Advancing age is associated with gene expression changes resembling mTOR inhibition: evidence from two human populations. *Mech Ageing Dev*. 2012;133:556-562.

27. Slagboom PE, Beekman M, Passtoors WM, et al. Genomics of human longevity. *Philos Trans R Soc Lond B Biol Sci*. 2011;366: 35-42.

28. Conover CA. Role of PAPP-A in aging and age-related disease [published online ahead of print July 10, 2012]. *Exp Gerontol.* doi:10.1016/j.exger.2012.06.017.

29. Harrington SC, Simari RD, Conover CA. Genetic deletion of pregnancy-associated plasma protein-A is associated with resistance to atherosclerotic lesion development in apolipoprotein E-deficient mice challenged with a high-fat diet. *Circ Res*. 2007;100: 1696-1702.

30. Conover CA, Mason MA, Levine JA, Novak CM. Metabolic consequences of pregnancy-associated plasma protein-A deficiency in mice: exploring possible relationship to the longevity phenotype. *J Endocrinol*. 2008;198:599-605.

31. Zakiyanov O, Kalousová M, Kratochvilová M, Kríha V, Zima T, Tesar V. Determinants of circulating matrix metalloproteinase-2 and pregnancy-associated plasma protein-A in patients with chronic kidney disease. *Clin Lab*. 2012;58:471-480.

32. Chung HY, Sung B, Jung KJ, Zou Y, Yu BP. The molecular inflammatory process in aging. *Antioxid Redox Signal*. 2006;8:572-581.

33. Collerton J, Martin-Ruiz C, Davies K, et al. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ Study. *Mech Ageing Dev*. 2012;133:456-466.

34. Brod S. Unregulated inflammation shortens human functional longevity. *Inflam Res*. 2000;49:561-570.

35. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908:24-54.

36. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med*. 2011;62:141-155.

37. Barrett L, Fowke KR, Grant MD. Cytomegalovirus, aging, and HIV: a perfect storm. *AIDS Rev*. 2012;14:159-167.

38. Stenvinkel P, Ketteler M, Johnson RJ, et al. Interleukin-10, IL-6 and TNF-α: important factors in the altered cytokine network of end-stage renal disease—the good, the bad and the ugly. *Kidney Int*. 2005;67:1216-1233.

39. Kuilman T, Michaloglou C, Vredeveld LC, et al. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. *Cell*. 2008;133:1019-1031.

40. Campisi J, d'Addadi Fagagna F. Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol*. 2007;8:729-740.

41. Acosta JC, O'Loghlen A, Banito A, et al. Chemokine signaling via the CXCR2 receptor reinforces senescence. *Cell*. 2008;133:1006-1018.

42. Tsirnpalis G. Cellular senescence, cardiovascular risk and CKD: a review of established and hypothetical interconnections. *Am J Kidney Dis*. 2007;51:131-144.

43. Banito A, Rashid ST, Acosta JC, et al. Senescence impairs successful reprogramming to pluripotent stem cells. *Genes Dev*. 2009;23:2134-2139.

44. Noh H, Yu MR, Kim HJ, et al. Uremia induces functional incompetence of bone marrow-derived stromal cells. *Nephrol Dial Transplant*. 2012;27:218-225.

45. Jourde-Chiche N, Dou L, Sabatier F, et al. Levels of circulating endothelial progenitor cells are related to uremic toxins and vascular injury in hemodialysis patients. *J Thromb Haemost*. 2009;7:1576-1584.

46. Merino A, Buendia P, Martin-Malo A, Aljama P, Ramirez R, Carracedo J. Senescent $CD14^{+}CD16^{+}$ monocytes exhibit pro-inflammatory and proatherosclerotic activity. *J Immunol*. 2011;186:1809-1815.

47. Sester U, Sester M, Heine G, Kaul H, Girndt M, Köhler H. Strong depletion of CD14(+)CD16(+) monocytes during haemodialysis treatment. *Nephrol Dial Transplant.* 2001;16:1402-1408.

48. Wu H, Chen H, Hu PC. Circulating endothelial cells and endothelial progenitors as surrogate biomarkers in vascular dysfunction. *Clin Lab*. 2007;53:285-295.

49. Girndt M, Seibert E. Premature cardiovascular disease in chronic renal failure (CRF): a model for an advanced ageing process. *Exp Gerontol*. 2010;45:797-800.

50. Vasa M, Fichtlscherer S, Aicher A, et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ Res*. 2003;89:E1-E7.

51. Li GQ, Yang Y, Ke DZ, et al. Association of circulating endothelial progenitor cells ($CD14^{+}$-EPC) with renal function in patients with coronary artery disease [published online ahead of print July 12, 2012]. *Clin Appl Thromb Hemost.*

52. Seidler S, Zimmermann HW, Bartneck M, Trautwein C, Tacke F. Age-dependent alterations of monocyte subsets and monocyte-related chemokine pathways in healthy adults. *BMC Immunol*. 2010;11:30.

53. Ramírez R, Carracedo J, Merino A, et al. $CD14^{+}CD16^{+}$ monocytes from chronic kidney disease patients exhibit increased adhesion ability to endothelial cells. *Contrib Nephrol*. 2011;171:57-61.

54. Carracedo J, Merino A, Briceño C, et al. Carbamylated low-density lipoprotein induces oxidative stress and accelerated senescence in human endothelial progenitor cells. *FASEB J*. 2011;25:1314-1322.

55. Chan CT, Li SH, Verma S. Nocturnal hemodialysis is associated with restoration of impaired endothelial progenitor cell biology in end-stage renal disease. *Am J Physiol Renal Physiol*. 2005;289:F679-F684.

56. Gely-Pernot A, Coronas V, Harnois T, et al. An endogenous vitamin K-dependent mechanism regulates cell proliferation in the brain subventricular stem cell niche. *Stem Cells*. 2012;30:719-731.

57. Cranenburg EC, Schurgers LJ, Uiterwijk HH, et al. Vitamin K intake and status are low in hemodialysis patients. *Kidney Int*. 2012;82:605-610.

58. Blackburn EH, Greider CW, Szostak JW. Telomeres and telomerase: the path from maize, Tetrahymena and yeast to human cancer and aging. *Nat Med*. 2006;12:1133-1138.

59. Cao K, Blair CD, Faddah DA, et al. Progerin and telomere dysfunction collaborate to trigger cellular senescence in normal human fibroblasts. *J Clin Invest*. 2011;121: 2833-2844.

60. Fyhrquist F, Saijonmaa O. Telomere length and cardiovascular aging. *Ann Med*. 2012;44(suppl 1):S138-S142.

61. Shiels PG, McGlynn LM, MacIntyre A, et al. Accelerated telomere attrition is associated with relative household income, diet and inflammation in the pSoBid cohort. *PLoS One*. 2011;6:e22521.

62. Andrews NP, Fujii H, Goronzy JJ, Weyand CM. Telomeres and immunological diseases of aging. *Gerontology*. 2010;56:390-403.

63. van de Berg PJ, Griffiths SJ, Yong SL, Macaulay R, et al. Cytomegalovirus infection reduces telomere length of the circulating T cell pool. *J Immunol*. 2010;184:3417-3423.

64. Ilmonen P, Kotrschal A, Penn DJ. Telomere attrition due to infection. *PLoS One*. 2008;3:e2143.

65. Fitzpatrick AL, Kronmal RA, Gardner JP, et al. Leukocyte telomere length and cardiovascular disease in the Cardiovascular Health Study. *Am J Epidemiol*. 2007;165:14-21.

66. O'Donovan A, Pantell MS, Puterman E, et al. Cumulative inflammatory load is associated with short leukocyte telomere length in the Health, Aging and Body Composition Study. *PLoS One*. 2011;6:e19687.

67. Kurz DJ, Decary S, Hong Y, Trivier E, Akhmedov A, Erusalimsky JD. Chronic oxidative stress compromises telomere integrity and accelerates the onset of senescence in human endothelial cells. *J Cell Sci*. 2004;117:17-26.

68. Tzanetakou IP, Katsilambros NL, Benetos A, Mikhailidis DP, Perrea DN. "Is obesity linked to aging?": adipose tissue and the role of telomeres. *Ageing Res Rev*. 2012;11:220-229.

69. Brouilette SW, Moore JS, McMahon AD, et al. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study. *Lancet*. 2007;369:107-114.

70. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet*. 2003;361:393-395.

71. Wills LP, Schnellmann RG. Telomeres and telomerase in renal health. *J Am Soc Nephrol*. 2011;22:39-41.

72. Ramírez R, Carracedo J, Soriano S, et al. Stress-induced premature senescence in mononuclear cells from patients on long-term hemodialysis. *Am J Kidney Dis*. 2005;45:353-359.

73. Carrero JJ, Stenvinkel P, Fellström B, et al. Telomere attrition is associated with inflammation, low fetuin-A levels and high mortality in prevalent haemodialysis patients. *J Intern Med*. 2008;263:302-312.

74. Westhoff JH, Schildhorn C, Jacobi C, et al. Telomere shortening reduces regenerative capacity after acute kidney injury. *J Am Soc Nephrol*. 2010;21:327-336.

75. Failla G. The aging process and cancerogensis. *Ann N Y Acad Sci*. 1958;71:1124-1140.

76. Dreesen O, Stewart CL. Accelerated aging syndromes, are they relevant to normal human aging? *Aging (Albany NY)*. 2011;3:889-895.

77. Niedernhofer LJ, Garinis GA, Raams A, et al. A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. *Nature*. 2006;444:1038-1043.

78. Vina J, Gambini J, Lopez-Grueso R, Abdelaziz KM, Jove M, Borras C. Females live longer than males: role of oxidative stress. *Curr Pharm Des*. 2011;17:3959-3965.

79. Seo AY, Joseph AM, Dutta D, Hwang JC, Aris JP, Leeuwenburgh C. New insights into the role of mitochondria in aging:

mitochondrial dynamics and more. *J Cell Sci*. 2010;123:2533-2542.

80. Hall AM, Unwin RJ. The not so 'mighty chondrion': emergence of renal diseases due to mitochondrial dysfunction. *Nephron Physiol*. 2007;105:1-10.

81. Tarng DC, Huang TP, Wei YH, et al. 8-Hydroxy-2′-deoxyguanosine of leukocyte DNA as a marker of oxidative stress in chronic hemodialysis patients. *Am J Kidney Dis*. 2000;36:934-944.

82. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant of uremia: oxidative stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int*. 2002;62:1524-1538.

83. Lans H, Hoeijmakers JHJ. Genomic stability, progressive kidney failure and aging. *Nat Genet*. 2012;44:836-838.

84. Kuro-o M, Matsumura Y, Aizawa H, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature*. 1997;390:45-51.

85. Schroff R, Shanahan CM. Klotho: an elixir of youth for the vasculature. *J Am Soc Nephrol*. 2011;22:5-7.

86. Shiraki-Iida T, Aizawa H, Matsumura Y, et al. Structure of the mouse klotho gene and its two transcripts encoding membrane and secreted protein. *FEBS Lett*. 1998;424:6-10.

87. Hu MC, Shi M, Zhang J, et al. Klotho deficiency causes vascular calcification in chronic kidney disease. *J Am Soc Nephrol*. 2011;22:124-136.

88. Sun C-Y, Chang S-C, Wu M-S. Suppression of klotho expression by protein-bound uremic toxins is associated with increased DNA methyltransferase expression and DNA hypermethylation. *Kidney Int*. 2012;81:640-650.

89. Liu L, van Groen T, Kadish I, et al. Insufficient DNA methylation affects healthy aging and promotes age-related health problems. *Clin Epigenet*. 2011;2:349-360.

90. Moreno JA, Izquierdo MC, Sanchez-Niño MD, et al. The inflammatory cytokines TWEAK and TNFα reduce renal klotho expression through NFκB. *J Am Soc Nephrol*. 2011;22:1315-1325.

91. Sugiura H, Tsuchiya K, Nitta K. Circulating levels of soluble α-klotho in patients with chronic kidney disease. *Clin Exp Nephrol*. 2011;15:795-796.

92. Hu MC, Shi M, Zhang J, et al. Klotho: a novel phosphaturic substance acting as an autocrine enzyme in the renal proximal tubule. *FASEB J*. 2010;24:3438-3450.

93. Chang Q, Hoefs S, van der Kemp AW, Topala CN, Bindels RJ, Hoenderop JG. The beta-glucuronidase klotho hydrolyzes and activates the TRPV5 channel. *Science*. 2005;310:490-493.

94. Chen TH, Kuro-O M, Chen CH, et al. The secreted klotho protein restores phosphate retention and suppresses accelerated aging in klotho mutant mice [published online ahead of print October 3, 2012]. *Eur J Pharmacol.* http://dx.doi.org/10.1016/j.ejphar.2012.09.032.

95. Yamamoto M, Clark JD, Pastor JV, et al. Regulation of oxidative stress by the anti-aging hormone klotho. *J Biol Chem*. 2005;280:38029-38034.

96. Maekawa Y, Ohishi M, Ikushima M, et al. Klotho suppresses TNF-alpha-induced expression of adhesion molecules in the endothelium and attenuates NF-kappaB activation. *Endocrine*. 2009;35:341-346.

97. Maekawa Y, Ohishi M, Ikushima M, et al. Klotho protein diminishes endothelial apoptosis and senescence via a mitogen-activated kinase pathway. *Geriatr Gerontol Int*. 2011;11:510-516.

98. Sugiura H, Yoshida T, Shiohira S, et al. Reduced klotho expression level in kidney aggravates renal interstitial fibrosis. *Am J Physiol Renal Physiol*. 2012;302:F1252-F1264.

99. Kurosu H, Yamamoto M, Clark JD, et al. Suppression of aging in mice by the hormone klotho. *Science*. 2005;309:1829-1833.

100. Olauson H, Lindberg K, Amin R, et al. Targeted deletion of klotho in kidney distal tubule disrupts mineral metabolism. *J Am Soc Nephrol*. 2012;23:1641-1651.

101. Urakawa I, Yamazaki Y, Shimada T, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. 2006;444:770-774.

102. Ohnishi M, Nakatani T, Lanske B, Razzaque MS. Reversal of mineral ion homeostasis and soft-tissue calcification of klotho knockout mice by deletion of vitamin D 1alpha-hydroxylase. *Kidney Int*. 2009;75:1166-1172.

103. Ohnishi M, Razzaque MS. Dietary and genetic evidence for phosphate toxicity accelerating mammalian aging. *FASEB J*. 2010;24:3562-3571.

104. Sitara D, Kim S, Razzaque MS, et al. Genetic evidence of serum phosphate-independent functions of FGF-23 on bone. *PLoS Genet*. 2008;4:e1000154.

105. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31:607-617.

106. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G; Cholesterol And Recurrent Events Trial Investigators. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation*. 2005;112:2627-2633.

107. Dhingra R, Sullivan LM, Fox CS, et al. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch Intern Med*. 2007;167:879-885.

108. Foley RN, Collins AJ, Herzog CAJ, Ishani A, Kalra PA. Serum phosphate and left ventricular hypertrophy in young adults: the Coronary Artery Risk Development in Young Adults Study. *Kidney Blood Press Res*. 2009;32:37-44.

109. Mathew S, Tustison KS, Sugatani T, Chaudhary LR, Leonard Rifas L, Hruska KA. The mechanism of phosphorus as a cardiovascular risk factor in CKD. *J Am Soc Nephrol*. 2008;19:1092-1105.

110. Kendrick J, Chonchol M. The role of phosphorus in the development and progression of vascular calcification. *Am J Kidney Dis*. 2011;58:826-834.

111. White KE, Larsson TE, Econs MJ. The roles of specific genes implicated as circulating factors involved in normal and disordered phosphate homeostasis: frizzled related protein-4, matrix extracellular phosphoglycoprotein, and fibroblast growth factor 23. *Endocr Rev*. 2009;27:221-241.

112. Larsson T, Nisbeth U, Ljunggren O, Jüppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney Int*. 2003;64:2272-2279.

113. Gutiérrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med*. 2008;359:584-592.

114. Mirza MA, Larsson A, Melhus H, Lind L, Larsson TE. Serum intact FGF23 associate with left ventricular mass, hypertrophy and geometry in an elderly population. *Atherosclerosis*. 2009;207:546-551.

115. Faul C, Ansel P, Behzad Oskouei A, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest*. 2011;121:4393-4408.

116. Lim K, Lu TS, Molostvov G, et al. Vascular klotho deficiency potentiates the development of human artery calcification and mediates resistance to fibroblast growth factor 23. *Circulation*. 2012;125:2243-2255.

117. Huang PH, Chen YH, Tsai HY, et al. Intake of red wine increases the number and functional capacity of circulating endothelial progenitor cells by enhancing nitric oxide bioavailability. *Arterioscler Thromb Vasc Biol*. 2010;30:869-877.

118. Morishita K, Shirai A, Kubota M, et al. The progression of aging in klotho mutant mice can be modified by dietary phosphorus and zinc. *J Nutr*. 2001;131:3182-3188.

119. Young H-H, Wu V-C. Klotho methylation is linked to uremic toxins and chronic kidney disease. *Kidney Int*. 2012;81:611-612.

120. Zhang H, Li Y, Fan Y, et al. Klotho is a target gene of PPAR-gamma. *Kidney Int*. 2008;74:732-739.

121. Mizuno I, Takahashi Y, Okimura Y, Kaji H, Chihara K. Upregulation of the klotho gene expression by thyroid hormone and during adipose differentiation in 3T3-L1 adipocytes. *Life Sci*. 2001;68:2917-2923.

122. Tang R, Zhou QL, Ao X, Peng WS, Veeraragoo P, Tang TF. Fosinopril and losartan regulate klotho gene and nicotinamide adenine dinucleotide phosphate oxidase expression in kidneys of spontaneously hypertensive rats. *Kidney Blood Press Res*. 2011;34:350-357.

123. Forster RE, Jurutka PW, Hsieh J-C, et al. Vitamin D receptor controls expression of the anti-aging klotho gene in mouse and human renal cells. *Biochem Biophys Res Commun*. 2011;414:557-562.

124. Olivieri F, Mazzanti I, Abbatecola AM, et al. Telomere/telomerase system: a new target of statins pleiotropic effect? *Curr Vasc Pharmacol*. 2012;10:216-224.

125. Lin J, Kroenke CH, Epel E, et al. Greater endogenous estrogen exposure is associated with longer telomeres in postmenopausal women at risk for cognitive decline. *Brain Res*. 2011;1379:224-231.

126. Sprouse AA, Steding CE, Herbert BS. Pharmaceutical regulation of telomerase and its clinical potential. *J Cell Mol Med*. 2012;16:1-7.

127. Richards JB, Valdes AM, Gardner JP, et al. Higher serum vitamin D concentrations are associated with longer leukocyte telomere length in women. *Am J Clin Nutr*. 2007;86:1420-1425.

128. Tilstra JS, Robinson AR, Wang J, et al. NF-κB inhibition delays DNA damage-induced senescence and aging in mice. *J Clin Invest*. 2012;122:2601-2612.

129. Coombes JS, Fassett RG. Antioxidant therapy in hemodialysis patients: a systematic review. *Kidney Int*. 2012;81:233-246.

130. Hutchison AJ, Smith CP, Brenchley PE. Pharmacology, efficacy and safety of oral phosphate binders. *Nat Rev Nephrol*. 2011;7:578-589.

131. Schiavi SC, Tang W, Bracken C, et al. Npt2b deletion attenuates hyperphosphatemia associated with CKD. *J Am Soc Nephrol*. 2012;23:1691-1700.

132. Hjelmborg B, Iachine I, Skytthe A, et al. Genetic influence on human lifespan and longevity. *Hum Genet*. 2006;119:312-321.

133. Deelen J, Uh HW, Monajemi R, et al. Gene set analysis of GWAS data for human longevity highlights the relevance of the insulin/IGF-1 signaling and telomere maintenance pathways. *Age (Dord)*. 2013;35:235-249.

134. Ostan R, Bucci L, Capri M, et al. Immunosenescence and immunogenetics of human longevity. *Neuroimmunomodulation*. 2008;15:224-240.

135. Arking DE, Krebsova A, Macek MS, et al. Association of human aging with a functional variant of klotho. *Proc Natl Acad Sci U S A*. 2002;99:856-861.

136. Deelen J, Beekman M, Uh HW, et al. Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. *Aging Cell*. 2011;10:686-689.

137. Weindruch R, Walford RL, Fligiel S, Guthrie D. The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. *J Nutr*. 1986;116:641-654.

138. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science*. 2009;325(5937):201-204.

139. Mattison JA, Roth GS, Beasley TM, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature*. 2012;489:318-321.

140. Trepanowski JF, Canale RE, Marshall KE, Kabir MM, Bloomer RJ. Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings. *Nutr J*. 2011;10:107.

141. Blagosklonny MV. Calorie restriction: decelerating mTOR-driven aging from cells to organisms (including humans). *Cell Cycle*. 2010;9:683-688.

142. Smith DL, Mattison JA, Desmond RA, et al. Telomere dynamics in rhesus monkeys: no apparent effect of caloric restriction. *J Gerontol A Biol Sci Med Sci*. 2011;66:1163-1168.

143. Noordam R, Gunn DA, Tomlin CC, et al. High serum glucose levels are associated with a higher perceived age. *Age (Dordr)*. 2013;35:189-195.

144. Lee JH, Jung KJ, Kim JW, Kim HJ, Yu BP, Chung HY. Suppression of apoptosis by calorie restriction in aged kidney. *Exp Gerontol*. 2004;39:1361-1368.

145. Hernandez-Corbacho MJ, Jenkins RW, Clarke CJ, et al. Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings. *PLoS One*. 2011;6:e20411.

146. Nakata R, Takahashi S, Inoue H. Recent advances in the study on resveratrol. *Biol Pharm Bull*. 2012;35:273-279.

147. Zhong L-M, Zong Y, Sun L, et al. Resveratrol inhibits inflammatory responses via the mammalian target of rapamycin signaling pathway in cultured LPS-stimulated microglial cells. *PLOS One*. 2012;7:e32195.

148. Cheng AS, Cheng YH, Chiou CH, Chang TL. Resveratrol upregulates Nrf2 expression to attenuate methylglyoxal-induced insulin resistance in Hep G2 cells. *J Agric Food Chem*. 2012;60:9180-9187.

149. Botden IP, Oeseburg H, Durik M, et al. Red wine extract protects against oxidative-stress-induced endothelial senescence. *Clin Sci*. 2012;123:499-507.

150. da Luz PL, Tanaka L, Brum PC, et al. Red wine and equivalent oral pharmacological doses of resveratrol delay vascular aging but do not extend life span in rats. *Atherosclerosis*. 2012;224:136-142.

151. Lagouge M, Argmann C, Gerhart-Hines Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell*. 2006;127:1109-1122.

152. Momken I, Stevens L, Bergouignan A, et al. Resveratrol prevents the wasting disorders of mechanical unloading by acting as a physical exercise mimetic in the rat. *FASEB J*. 2011;25:3646-3660.

153. Chen KH, Cheng ML, Jing YH, Chiu DT, Shiao MS, Chen JK. Resveratrol ameliorates metabolic disorders and muscle wasting in streptozotocin-induced diabetic rats. *Am J Physiol Endocrinol Metab*. 2011;301:E853-E863.

154. Hallows WC, Smith BC, Lee S, Denu JM. Ure(k)a! Sirtuins regulate mitochondria. *Cell*. 2009;137:404-406.

155. Charansonney OL. Physical activity and aging: a life-long story. *Discov Med*. 2011;12:177-185.

156. Du M, Prescott J, Kraft P, et al. Physical activity, sedentary behavior, and leukocyte telomere length in women. *Am J Epidemiol*. 2012;175:414-422.

157. Farzaneh-Far R, Lin J, Epel ES, Harris WS, Blackburn EH, Whooley MA. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. *JAMA*. 2010;303:250-257.

158. Ubeda N, Achón M, Varela-Moreiras G. Omega 3 fatty acids in the elderly. *Br J Nutr*. 2012;107(suppl 2):S137-S151.

159. Stenvinkel P. Can treating persistent inflammation limit protein energy wasting? [published online ahead of print October 9, 2012] *Semin Dial.* doi: 10.1111/sdi.12020.

160. Blagosklonny MV. Prospective treatment of age-related diseases by slowing down aging. *Am J Pathol*. 2012;181(4):1142-1146.

161. Selman C, Patridge L. A double whammy for aging? Rapamycin extends lifespan and inhibits cancer in inbred female mice. *Cell Cycle*. 2012;11:17-18.

162. Chen C, Liu Y, Liu Y, Zhen GP. mTOR regulation and therapeutic rejuvenation of aging hematopoietic stem cells. *Sci Signal*. 2009;2(98):ra75.

163. Ungar L, Harari Y, Toren A, Kupiec M. TOR complex 1 controls telomere length by affecting the level of Ku. *Curr Biol*. 2011;21:2115-2120.

164. Mendelsohn AR, Larrick JW. Rapamycin as an antiaging therapeutic? Targeting mammalian target of rapamycin to treat Hutchinson-Gilford progeria and neurodegenerative diseases. *Rejuvenation Res*. 2011;14:437-441.

165. Del Barco S, Vazquez-Martin A, Cufí S, et al. Metformin: multi-faceted protection against cancer. *Oncotarget*. 2011;2:896-917.

166. Tsujikawa H, Kurotaki Y, Fujimori T, Fukuda K, Nabeshima Y. Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system. *Mol Endocrinol*. 2003;17:2393-2403.

167. Zoccali C, Ruggenenti P, Perna A, et al. Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. *J Am Soc Nephrol*. 2011 22:1923-1930.

168. Shuto E, Taketani Y, Tanaka R, et al. Dietary phosphorus acutely impairs endothelial function. *J Am Soc Nephrol*. 2009;20:1504-1512.

169. Al-Aly Z. Phosphate, oxidative stress, and nuclear factor-κB activation in vascular calcification. *Kidney Int*. 2011;79:1044-1047.

170. Smith ER, Ford ML, Tomlinson LA, Rajkunar C, McMahon LP, Holt SG. Phosphorylated fetuin-A-containing calciprotein particles are associated with aortic stiffness and a procalcific milieu in patients with pre-dialysis CKD. *Nephrol Dial Transplant*. 2012;27:1957-1966.

171. Block GA, Wheeler DC, Persky MS, et al. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol*. 2012;23:1407-1415.

172. Bergwitz C. Dietary phosphate modifies lifespan in *Drosophila*. *Nephrol Dial Transplant*. 2012;27:3399-3406.