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Out of control: accelerated aging in uremia

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Abstract

Next to a high morbidity, patients with end-stage renal failure (ESRD) suffer from a complex spectrum of clinical manifestations. Both the phenotype of patients with ESRD as well as the pathophysiology of uremia show interesting parallels with the general aging process. Phenotypically, patients with ESRD have an increased susceptibility for both cardiovascular as well as infectious disease and show a reduction in functional capacity as well as muscular mass (sarcopenia), translating into a high prevalence of frailty also in younger patients. Pathophysiologically, the immune dysfunction, telomere attrition and the presence of low-grade inflammation in uremic patients also show parallels with the aging process. System models of aging, such as the homeodynamic model and reliability theory of Gavrilov may also have relevance for ESRD. The reduction in the redundancy of compensatory mechanisms and the multisystem impairment in ESRD explain the rapid loss of homeodynamic/homeostatic balance and the increased susceptibility to external stressors in these patients. System theories may also explain the relative lack of success of interventions focusing on single aspects of renal disease. The concept of accelerated aging, which also shares similarities with other organ diseases, may be of relevance both for a better understanding of the uremic process, as well as for the design of multidimensional interventions in ESRD patients, including an important role for early rehabilitation. Research into processes akin to both aging and uremia may result in novel therapeutic approaches.

Keywords: accelerated aging; inflammation; malnutrition; sarcopenia; uremia

In contrast to the general population, patients with end-stage renal disease (ESRD) have experienced a different life course which is characterized by progressive damage in various vital organs such as the kidney, bones, heart and vasculature, which already starts before the onset of dialysis treatment [1]. In addition, the life trajectories of ESRD patients include significant transition periods such as the preparation for and start of dialysis, change of treatment modalities and transplant failure, which cause physical, mental as well as physiological distress [2, 3].

Clinical acumen indicates that ESRD patients are generally biologically older compared with non-ESRD fellow citizens of similar calendarial ages. Although accelerated aging is clinically evident in the majority of ESRD patients, it has received relatively little attention in the literature [4–8]. One of the underlying reasons might be that the biological age is difficult to quantify. Therefore, in order to identify the phenotype of accelerated aging in ESRD patients properly, it is first necessary to provide solid arguments for its existence. After having done so, this review will discuss potential mechanisms for and consequences of accelerated aging in uremia. In this respect, it is relevant to look at recent systemic models developed for understanding the aging process, which have interesting analogies with pathophysiological as well as phenotypical alterations in ESRD patients. These models may have relevance for a better understanding of the uremic process and might provide some explanation for the relative paucity of randomized trials demonstrating effective interventions in dialysis patients.

The phenotype of accelerated aging in uremia

The phenotype of biological aging is defined along various lines in the relevant literature (http://www.senescence.info/aging_definition.html). The *first* hallmark of accelerated aging is the exponential increase in mortality in dialysis patients when compared with the general population at similar calendarial ages. In order to express this increase in mortality numerically, statistical methods, such as the Gompertz model, are used, in which the mortality at a given age [$m(t)$] is expressed as $m(t) = A\,e^{ct}$, with A defined as the baseline mortality rate (usually set at adolescence), t as the time and c as the age-dependent mortality rate (A and c being population-specific parameters).

Although the increase in mortality of dialysis patients at any given age is clearly higher when compared with non-uremic controls, only one study applied the Gompertz function to compare the respective senescence rates

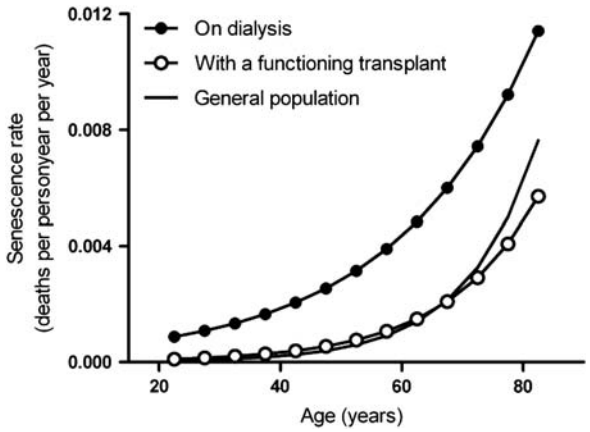

Fig. 1. Age-specific senescence rates of dialysis patients (using the derivative of the Gompertz equation) when compared with transplant patients and the general population (from ref. 9; with permission; Wiley and Sons).

between both populations. This study showed that using the first derivative of the Gompertz function, $m'(t) = Ac\ e^{ct}$ was a more meaningful approach for representing the accelerated aging in dialysis patients than the original Gompertz equation [9] (Figure 1). The *second* hallmark of aging is an increased susceptibility to disease. Large surveys comparing the general and ESRD populations show that the risk of cardiovascular as well as infectious morbidity and mortality is greatly increased in the latter [10, 11]. Using simple graphical comparison, the relative risk for cardiovascular mortality of a 25–34-year-old dialysis patient is comparable with that of the general population of >75 years of age [10]. A comparable figure was recently shown for infection-related mortality [12]. Mortality from pulmonary infections is increased 12–14-fold in the dialysis population [12, 13]. The *third* hallmark of aging is reduced physical capacity. Various studies have shown a reduced exercise capacity as well of loss of skeletal muscle mass (sarcopenia) and subsequent loss of muscle strength in dialysis patients in contrast to age-matched controls [14–16]. The reduced physical capacity and the loss of muscle mass are associated with a high prevalence of frailty. Phenotypically, frailty is a clinical syndrome characterized by multiple pathologies, such as weight loss, fatigue, weakness, low activity, slow motor performance and balance and gait abnormalities [17]. Whereas in the general population the frailty syndrome is mainly encountered in geriatric patients, a recent study showed that the frailty phenotype was highly prevalent already in young dialysis patients. Of concern, 44% of dialysis patients below 40 years of age were classified as frail [18].

With regard to other organ systems, there are similarities between the vascular wall abnormalities observed in aging non-uremic subjects and those in younger dialysis patients [7], and the prevalence of cognitive impairment is high (30–40%) even in middle-aged dialysis patients [19].

In summary, there are various arguments for the existence of a phenotype of accelerated aging in dialysis patients.

Pathophysiology of accelerated aging in uremia

The pathophysiology of the accelerated aging process in dialysis patients is multifactorial. Several pathogenetic factors identified in theories of aging have also been observed in the dialysis population, such as telomere loss, accumulation of advanced glycation end products (AGEs) and increased oxidative stress when compared with age-matched controls [4, 20–23]. The accelerated aging process and the high prevalence of frailty are not unique for uremia, but are also encountered in other chronic diseases such as HIV-related disorders and chronic obstructive pulmonary disease [24–26]. A common factor in uremia as well as other chronic diseases is the presence of low-grade inflammation. This is analogous to the situation in the general population, where the frailty phenotype and the aging process are also accompanied by low-grade inflammation [26–30]. In frail non-uremic subjects, increased plasma levels of interleukin (IL)-6 and the up-regulation of the transcription factor NF-kappa B are observed [26], consistent with findings in uremic patients [31] and likely important contributory factors to sarcopenia [16, 26, 32]. Moreover, oxidative stress and inflammation may be central causative factors in cell senescence, as suggested by their relation to telomere length [21–23]. Oxidative stress, inflammation and accumulation of AGEs, which are related to ageing in the general population, are also strongly involved in the pathogenesis of functional and structural cardiovascular abnormalities in renal patients [20, 21, 23, 27, 33].

Aging as well as uremia are accompanied by immune dysfunction. With regard to innate immunity, dendritic cell dysfunction is observed both in uremic patients and in non-uremic aging subjects, leading to chronic inflammation on one hand and impaired capacity to activate T cells on the other [12, 34, 35]. The adaptive immune system in uremic patients is on one hand characterized by an activated state, as reflected by the increase in IL-17 producing effector memory T cells as well as by functional impairment, concomitant with a reduction in naïve T cells. This is analogous to findings in non-uremic aging subjects [36–38]. Also, evidence for mononuclear cell senescence, characterized by reduced telomere length and proinflammatory activity, was found in dialysis patients [22].

More specific for renal failure is the potential relation between accelerated aging and abnormalities in mineral metabolism. Patients with renal failure are characterized by a reduced expression of Klotho, which is not only related to FGF23 resistance and abnormalities in mineral metabolism, but also to accelerated aging in *Klotho* $^{-/-}$ mice [5]. Of interest is also that vitamin D deficiency in the general population has been identified as a culprit for frailty, in addition to its relation with oxidative stress, telomere attrition and immune dysfunction [39].

Also specific for renal failure is the accumulation of protein-bound toxins such as indoxyl sulfate, which may be implicated in endothelial cell senescence and dysfunction through oxidative stress and p53-dependent apoptotic pathways [40, 41]. Possibly, also the dialysis treatment itself may contribute to accelerated aging. Apart from

inducing cardiovascular stress, dialysis might also contribute to inflammation and has been shown to contribute to monocyte senescence and apoptosis [22,42,43]. In this context, dialysate purity, the dialysis membrane and the loss of residual renal function likely play an important role [22, 43].

Possibly, the effect of dialysis on inflammation, cardiovascular function and cell senescence, which might contribute to accelerated aging in uremic patients, may explain the apparent contradictory finding that an earlier start of dialysis, resulting in improved uremic control does not result in an improvement in the outcome [44]. This is in sharp contrast to the beneficial effects of preemptive transplantation [45], which results in a far greater improvement in uremic control but also obviates the need for dialysis with its potential adverse effects.

Of importance is that recent observations also identify physical inactivity as not only a consequence but also a potential culprit in an accelerated aging process [46]. There is a strong relation between sarcopenia and physical inactivity in renal patients [15, 30]. Moreover, physical inactivity may lead to a reduction in the physiological reserve of the patient and thus increase the vulnerability to external stressors. In addition, physical inactivity may contribute to insulin resistance in skeletal muscle as well as inflammation [46].

Thus, it is tempting to speculate whether important clinical manifestations, such as the malnutrition–inflammation–atherosclerosis syndrome might actually be part of the broader multidimensional process of accelerated aging characteristic of uremia. In non-uremic aging subjects, a relation between frailty, inflammation and cardiovascular disease has been observed [47].

In the accelerated aging process, metabolic alterations, systemic inflammation, relative immune dysfunction, oxidative stress, sarcopenia, malnutrition, functional deterioration, uremia and comorbidity are likely mutually reinforcing factors in a vicious cycle (Figure 2). While some of these factors are unique for renal failure, the majority of these factors have important similarities with other chronic disease

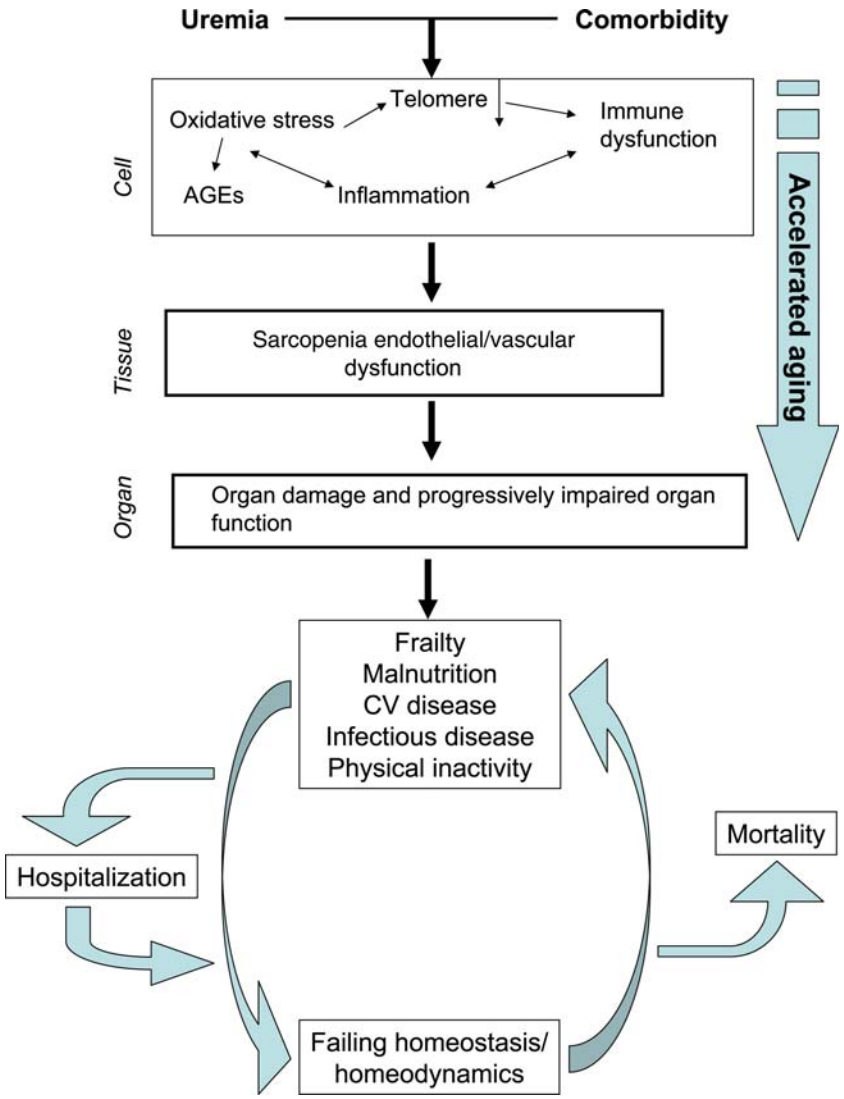

Fig. 2. Mechanisms and consequences of accelerated aging in uremia.

states and may thus be a more general manifestation of illness.

System models of aging applicable to uremia

In the following paragraphs, we discuss two systemic models for aging, which might have relevance for renal disease [48, 49]. The first is the homeodynamic model proposed by F. Eugene Yates. In contrast to homeostasis, which appears to reflect a more static environment, the concept of homeodynamics is defined as the dynamic response of the organism to a continuously changing environment. The homeodynamic response depends on multilevel compensatory mechanisms with a high degree of complexity, which increases the diversity of responses to external stressors. These compensatory mechanisms depend on the timely availability of Gibbs free energy produced by metabolic networks.

An important characteristic of the homeodynamic approach is the coupling of non-linear oscillatory networks, such as heart rate, autonomic nervous system and respiration. As an example, variability of sinus node discharge is associated with a higher resilience to pathological arrhythmias when compared with a completely regular sinus rhythm [50]. In patients with ESRD, an uncoupling of physiologic processes is indeed frequently observed [51]. In the homeodynamic theory, the aging process is defined as an uncoupling of physiologic processes, a reduction in complexity and a compromised availability of Gibbs free energy from metabolic networks. These factors might result in an impaired ability for the organism to respond to an external stressor [48, 52]. In other words, the diversity of homeodynamic responses is reduced, resulting in less fine-tuned reactions to the challenges of second-to-second-changing internal and external environments and an eventually reduced tolerance to stressors, reduced functional reserve and an increased likelihood of failure of homeostatic mechanisms. This concept is in agreement with the pathophysiological definition of frailty [30, 53]. A reduced tolerance to external stressors and reduced functional reserve are frequently observed in the daily clinical care of dialysis patients and also show in the increased incidence of cardiovascular and infectious complications [12]. Conventional dialysis techniques are only partly able to restore the flexibility of the body to respond to environmental demands. The insufficient correction of the internal environment may contribute to a vicious cycle by increasing the vulnerability to stressors. As an example, overhydration may lead to impaired cardiac performance, which in itself increases the susceptibility to symptomatic fluid overload and inflammation [54, 55].

The homeodynamic theory of aging has parallels with the reliability or system theory of aging: in reliability theory, degradation failures are characterized by a gradual loss of proper functioning of interconnected subsystems (such as organs) and their components (such as cells), whereas catastrophic failure corresponds to the end of life of a system or its components [49]. The failure risk of the system increases with age. One of the most frequently used models in system failure is the aforementioned Gompertz equation, which also has relevance for patients with renal failure as discussed previously. The advantage of the reliability theory is that it has a sound mathematical basis, which allows quantitative statements; noteworthy, this theory is largely unexplored in ESRD patients [49, 56].

Early in life, system failure is prevented by a redundancy of compensatory mechanisms and system components; aging is characterized by a loss of redundancies. An example relevant to patients with renal failure is a reduction in endothelial progenitor cells, resulting in impaired vascular repair [41], and a loss of muscle cells, resulting in sarcopenia [49]. Near the end of life, a catastrophic system breakdown may occur because of an avalanche-like destruction, resulting from a cascade of failures in interdependent subsystems. In dialysis patients, this has clinical parallels with the exponential rise in hospitalization rates before death which we recently observed (Usvyat L. EDTA-ERA conference, 2012). In the context of progressive failures of one of the key homeostatic/homeodynamic subsystems (the kidney) and many components in other subsystems (such as the vasculature and skeletal muscle), reliability theory offers explanations why dialysis patients are highly vulnerable to external stressors. The reliability theory also explains the interconnection between the failures of different subsystems, as clinically evident in the rise in hospitalizations for cardiovascular causes following admission for an infectious disease [57].

Can reliability theory help to explain some puzzling results in dialysis research?

It is tempting to speculate that increased sensitivity to external stressors in very frail patients explains the rapid decline in functional status and high mortality observed in elderly nursing home patients [58]. In these very frail patients, dialysis might act as an important external stressor [3], actually triggering a rapid 'system' breakdown. Moreover, system theories might provide a conceptual explanation for the fact why interventions focusing on a single aspect, such as treatment with statins (4D), use of high-flux filters, an increase in dialysis dose or hemodiafiltration or treatment with cinacalcet have failed to translate into substantially improved outcomes [59,60 http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1703773]. We propose that an explanation for these observations resides in the fact that ESRD is a state of both multisystem and component failure, whereas interventions directed primarily toward one of these contributing mechanisms may not result directly in major improvements in the outcomes.

Potential therapeutic implications of accelerated aging in uremia

The 'failures' of recent interventional studies with regard to improvements in mortality should by no means lead to defeatism in the treatment of these patients, because it is

likely that interventions targeting multiple aspects are of great clinical relevance. The goal should therefore be to optimize medical, dialysis and supportive therapy in all their aspects. An important argument for this hypothesis is the fact that extended or more frequent dialysis treatments, which lead to improvements of multiple targets (such as phosphate, toxin removal, fluid and blood pressure), do appear to result in improved outcomes [61]. Translated into the language of the reliability theory, an interesting example for component restoration is the improvement of endothelial progenitor-like cell function with nocturnal hemodialysis [62], which can be considered a multidimensional intervention given its effect on multiple components leading to a 'system improvement'. Moreover, the concept of accelerated aging may provide additional support for interventions directed at underlying processes, such as oxidative stress, accumulation of AGEs and inflammation. In addition, although an effect on mortality still needs to be demonstrated, data from uremic patients as well as from patients with other organ diseases show that active rehabilitation leads to significant increases in quality of life and physical performance [14, 15, 63]. Another implication is that interventions in geriatric patients and patients with chronic diseases may have direct relevance for the treatment of ESRD patients.

Some unresolved issues

Although the relation between uremia and accelerated aging provides an interesting additional conceptual framework for uremia, various unresolved issues remain. First, it is unknown when this process starts, although it is likely early in renal failure given the fact that, for example, abnormalities in mineral metabolism and inflammation are already detected long before the onset of ESRD [5, 64]. Second, it is important to distinguish the effects of uremia *per se* from those of comorbidity. To that end, studies early in the course of chronic kidney disease are necessary. It may be hypothesized that in early secondary forms of CKD (such as diabetes and nephrosclerosis), more signs of accelerated aging are observed compared with primary forms, given the fact that more system components may be affected in early secondary CKD. Third, it should also be noted that a substantial proportion of elderly dialysis patients may not show signs of accelerated aging when compared with age-matched controls. In the study of Johansen, 20% of octogenarians on dialysis did not fulfill the criteria for frailty [18]. Whether or not certain genetic polymorphisms provide protective or deleterious effects in dialysis patients is the subject of ongoing studies [65, 66]. Fourth, if dialysis treatment *per se* were a contributing factor to accelerated aging, the observed beneficial effects of frequent dialysis would appear paradoxical. We propose that in this case, the tradeoff between the potential adverse effects of dialysis is far outweighed by the beneficial effects of long or more frequent dialysis sessions on fluid state and uremic control together with the low ultrafiltration rates resulting in reduced circulatory stress. Lastly, although the systemic theories of aging provide an interesting and stimulating alternative framework to approach uremia, it is challenging to translate the components in these theories into meaningful (patho)physiological or psychological constructs upon which interventions can be based.

Conclusion

There are many convincing similarities between the uremic state and aging, suggesting that, in analogy to other chronic diseases, uremia indeed resembles a state of accelerated aging. A corollary is that next to the pathophysiological effects of the failing kidney function, uremia is a model of chronic disease. Although the traditional reductionist approach, studying individual components of the body affected by uremia, has brought us a long way, also a system-oriented approach is likely to result in novel insights. The concept of accelerated aging is such a system-oriented approach, which links processes observed in aging individuals to those observed in uremic patients. The concept that uremia is a state of accelerated aging results in testable quantitative hypotheses. For example, it would predict that multidimensional rather than one-dimensional interventions are more likely to be successful. Moreover, it would support the relevance of early rehabilitation programs for patients with renal disease in all age classes. Such a program could be relevant for both uremic patients as well as patients with other chronic diseases and thus need not be developed exclusively for renal patients. The concepts of accelerated aging also suggest that interventions studied in geriatric medicine may also be of relevance to the nephrologist [67]. Research into processes akin to both aging and uremia may result in novel therapeutic approaches.

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