Full Reviews

Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies

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ABSTRACT

Muscle wasting (or sarcopenia) is a common feature of the uremic phenotype and predisposes this vulnerable patient population to increased risk of comorbid complications, poor quality of life, frailty and premature death. The old age of dialysis patients is in addition a likely contributor to loss of muscle mass. As recent evidence suggests that assessment of muscle strength (i.e. function) is a better predictor of outcome and comorbidities than muscle mass, this opens new screening, assessment and therapeutic opportunities. Among established treatment strategies, the benefit of resistance exercise and endurance training are increasingly recognized among nephrologists as being effective and should be promoted in sedentary chronic kidney disease patients. Testosterone and growth hormone replacement appear as the most promising among emerging treatments strategies for muscle wasting. As treatment of muscle wasting is difficult and seldom successful in this often old, frail, sedentary and exercise-hesitant patient group, novel treatment strategies are urgently needed. In this review, we summarize recent studies on stimulation of mitochondrial biogenesis, myogenic stem (satellite) cells and manipulation of transforming growth factor family members, all of which hold promise for more effective therapies to target muscle mass loss and function in the future.

Keywords: dialysis, exercise, growth hormone, inflammation, muscle wasting, sarcopenia

INTRODUCTION

Skeletal muscle, accounting for 40% of body weight and 50% of body protein [1], is a major physiological reserve that is called upon when renal function declines. Skeletal muscle mass is tightly regulated because each component of total protein plays a critical role that is essential for survival; muscle is broken down when proteins or amino acids are needed, and because excess protein is not stored, continuous and sufficient dietary protein intake is necessary. Therefore, protein is an essential component of all cells and includes the visceral organs, blood cells, connective tissue, enzymes and antibodies [1]. Because proteins are associated with critical functions, these functions are impaired when protein is catabolized. As a consequence, strong associations between surrogates of muscle mass and survival are found in patients with chronic kidney disease (CKD) [2]. Moreover, body size and composition are significantly associated with physical functioning and quality of life [3]. This review aims to summarize our current understanding of established, emerging and novel treatment strategies that may benefit CKD patients subjected to muscle wasting. Aspects of etiology [4], assessment [5], mechanisms [6] and prevention [7] of protein energy wasting (PEW) in CKD patients have recently been thoroughly reviewed (Figures 1 and 2).
Correct Assessment of Muscle Mass: A Prerequisite for Treatment

A major difficulty in the development of effective therapies against muscle loss and strength is the rather imprecise and/or expensive methods available to assess changes in muscle mass during interventions. Another problem is that the prevalence of muscle wasting is hard to determine due to lack of established definitions. Skeletal muscle mass can be assessed by magnetic resonance imaging (MRI), computed tomography (CT) or dual-energy x-ray absorptiometry (DXA). Functional tests, such as handgrip strength and gait speed, are commonly used to assess muscle strength. As the turnover of cellular proteins is estimated to be \( \sim 1.0-1.5 \) kg of muscle \(^8\), a decrease in protein synthesis and/or an increase in protein degradation can have major effects on muscle mass. Even with minor losses in muscle contractile proteins (i.e. myosin, actin), force decrements are likely affected due to a reduction in cross-bridge formation during muscle contractions. Imaging methods or estimates of lean body mass, such as CT scans, may not evidence this. Thus, functional deficits may precede noticeable losses in muscle mass before these can be detected by conventional/current methods.

One complementary approach to the determination of anabolic/catabolic balance of practical significance for the nephrologist is the use of serum biomarkers. On the list of potential biomarkers to assess changes in muscle mass, serum creatinine may be an appropriate surrogate of muscle mass in end-stage renal disease (ESRD) patients when residual renal function is lost or minimal. Although reference values are difficult to ascertain given its dependency on muscle stores for each individual, creatinine may be useful for the detection of short-term changes, which would denote muscle mass losses.

Figure 1: Flow schedule showing how risk factors increase risk for loss of muscle mass and muscle strength in patients with CKD.

Figure 2: Loss of muscle mass and strength increase risk of various comorbid complications and premature death.

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Among novel biomarkers to estimate muscle mass, the N-terminal propeptide of type III procollagen (P3NP) is of interest as it is released into circulation during collagen synthesis [9].

**AGING: A MAJOR CONFOUNDER WHEN LOSS OF MUSCLE MASS IS EVALUATED IN CKD**

With age, changes of body composition occur, mainly involving a progressive loss of skeletal muscle mass with ensuing loss of muscle strength/function. It has been estimated that muscle mass declines at the rate of about 1.0–1.5% per year after 30 years of age. In parallel, total body fat increases, mostly in the abdominal area [10]. This condition has been classically named ‘sarcopenia of aging’ [11] and associated with frailty, cachexia and functional disability, leading to worsening of quality of life and risk of mortality. Although conceptually appealing, we must acknowledge that early and often unnoticed, unknown illnesses are highly prevalent in the advanced years when sarcopenia becomes evident, so may the isolation of ‘primary age-related sarcopenia’ be complex. Although the catabolic association of uremia and muscle loss is undeniable, the in general old age of dialysis patients should also be taken into account. How much of the muscle mass loss observed in the dialysis population is due to kidney disease *per se* and how much due to primary ageing is difficult to disentangle. A recent National Health and Nutrition Examination Survey (NHANES) report of 11,643 individuals who underwent DXA studied the association between sarcopenia and CKD stages [12]. They found an almost linear crude association between sarcopenia and renal function, but the association flattened out when standardizing by age. It is possible that differences in the prevalence of sarcopenia in this study might just reflect differences in the age distribution of patients with and without CKD. Comparing sarcopenia prevalence in dialysis populations with age- and sex-matched controls is hampered by the lack of such reference materials as well as disagreement among the different geriatric societies in deciding reference cutoffs. The decision is not inconsequential as the prevalence of sarcopenia in the NHANES adults varied up to 20-fold depending on the different research definitions available in the literature [13]. Taken together, there is a need to establish consensus criteria that can be reliably applied across clinical and research settings when prevalence of muscle loss is studied in the context of CKD.

**SHOULD NEPHROLOGISTS ASSESS MUSCLE STRENGTH RATHER THAN MUSCLE MASS?**

Although muscle mass is the strongest determinant of muscle function and strength, recent clinical data suggest that both entities are not solely dependent on each other [14, 15]. It seems apparent from population studies that as we grow old, muscle function and muscle quality worsen more rapidly than muscle mass. A recent Japanese study in a community-dwelling population showed that whereas age-related decreases in muscle mass were found trivial, the quality of muscle decreased progressively with aging in both sexes [16]. The mechanisms behind this disassociation are not fully evident but may relate to increased muscle fibrosis, alterations in contractile quality, neural activation and systemic inflammation. Fatness and sarcopenia have been found to exert a synergistic negative impact on physical performance among the elderly [17], and an interplay between both body compartments on muscle functionality can exist. It has been proposed that intramuscular fat infiltration may explain the loss of muscle function with age. Intramuscular adipose tissue infiltration by MRI was found to be greater in CKD patients than for age-sex-matched controls [18]. Altogether, this evidence may indicate that risk factors for the loss of muscle mass may not be the same as those for the loss of muscle functionality.

**ESTABLISHED TREATMENTS FOR LOSS OF MUSCLE MASS IN CKD**

At present, prevention and treatment of uremic muscle wasting should be based on optimal nutritional support [5] and correction of acidosis [6]. Another cornerstone of established treatment strategies for muscle loss is physical exercise [19], which will be discussed in more detail.

**Effects of physical exercise**

Among the established treatment options to prevent muscle wasting in ESRD patients, resistance exercise (RE) training appears to be the most effective [20]. Unfortunately, as this frail and sedentary patient population often exhibits comorbid conditions, such as osteoporosis, heart failure and anemia, they tend to avoid exercise. Nevertheless, RE training has been proven safe, feasible and well tolerated in various clinical settings including outpatient clinic [21], home-based regimes [22] and programs concomitant to dialysis [23]. Although the acute muscle response to RE appears intact in ESRD [24], long-term studies indicate a hampered effect of training when compared with healthy, older individuals [23, 25]. This suggests that RE, despite representing a robust acute anabolic stimulus in these patients, ought to be combined with other interventions aiming at normalizing protein homeostasis also in between exercise bouts.

Interestingly, several studies have reported substantial gains in muscle function also following aerobic (or endurance) or combined exercise-centered training, classically not considered to increase muscle strength. This phenomenon is most likely due to the severely deconditioned state of the muscle and stresses the need for regular exercise in this patient group. For example, leg cycling during hemodialysis (HD) improves not only cardiopulmonary fitness and endurance but also muscle strength, power, fatigability and physical function [26]. Similarly, a 12-week/24-session combined cardiovascular and RE program in CKD Stage 3–4 patients improved physical capacity and quality of life [20]. Moreover, a recent study provides compelling evidence that regular moderate-intensity aerobic exercise is safe with regard to immune and inflammatory responses and has the potential to be an effective anti-inflammatory therapy in CKD [27]. In accordance, Gielen *et al.* [28] showed that exercise training...
significantly reduced the local expression of tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6 and inducible nitric oxide synthase (iNOS) in skeletal muscle of congestive heart failure (CHF) patients.

Irisin is a peroxisome proliferator-activated receptor co-activator 1-α (PGC-1α)-dependent and exercise-responsive myokine with the potential to induce murine brown-fat-like development of white adipose tissue [29]. Whereas chronic training enhances irisin production in mice [29], the results have been conflicting in humans [30, 31]. As irisin serum concentrations decrease with reduced renal function [32], further studies exist [33], the role of irisin as a potential exercise hormone is unresolved issues regarding the characterization of irisin still malize irisin levels in CKD patients. However, as many unresolved issues regarding the characterization of irisin still exist [33], the role of irisin as a potential exercise hormone is unsettled. Nevertheless, the development of exercise mimetics (i.e. stimulators of nuclear receptors that regulate skeletal muscle energy metabolism and exercise-induced muscle remodeling) to enhance or substitute for the beneficial effects of physical exercise in the frail and ‘exercise-hesitant’ CKD patient population could be of clinical benefit [34]. However, it is likely that such agents will amplify the beneficial effects of regular exercise rather than becoming the sole therapeutic modality. As the emerging field of exercise epigenomics is expected to prosper and delineate mechanisms by which exercise confers a healthier phenotype and improves performance [35], this field may also add to treatment possibilities in dialysis patients.

**Table 1. Established, emerging and potential novel future treatment strategies for uremic muscle-wasting syndrome**

<table>
<thead>
<tr>
<th>A. Established treatment strategies of muscle loss</th>
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<tr>
<td>Nutritional supplementation [36]</td>
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<td>Correction of acidosis with sodium bicarbonate [37]</td>
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<td>Physical exercise [19–21]</td>
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<tr>
<td>Treatment of comorbidities that promote muscle mass loss, such as CHF, malignancies, depression and infections [7]</td>
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<td>Avoid glucocorticoid treatment [38]</td>
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<td>B. Emerging treatment strategies of muscle loss</td>
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<td>Testosterone, androgens [7, 39]</td>
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<td>Vitamin D [40]</td>
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<td>GH (rhGH) [41, 42]</td>
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<td>C. Potential future treatment strategies of muscle loss</td>
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<tr>
<td>Stimulation of mitochondrial biogenesis (sirtuins) [43]</td>
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<td>miRNAs [6, 44]</td>
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<td>Myogenic stem (satellite) cells [45]</td>
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<td>Manipulation of TGF-β superfamily members, such as inhibition of GDF8 and stimulation of GDF11 [46, 47]</td>
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<td>Targeting pro-inflammatory cytokines, such as IL-1, IL-6 and TFN [7, 48]</td>
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<td>Targeting the epigenome [49]</td>
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**EMERGING TREATMENTS FOR LOSS OF MUSCLE MASS IN CKD**

Emerging evidence suggests that hormonal supplementation with testosterone, vitamin D, insulin growth factor (IGF-1) and growth hormone (GH) may have beneficial effects on the uremic muscle-wasting syndrome (Table 1).

**Testosterone**

Hypogonadism is a frequent endocrine disorder in men undergoing dialysis, which associates with sexual disorders, worse quality of life, poor graft survival and increased mortality risk [50]. In view of its physiological effects as an anabolic hormone, hypogonadal men on dialysis have been shown to require higher erythropoiesis-stimulating agent dosages [51] and to present with both lower muscle mass and strength independent of age [52], comorbid conditions or medications that impact testosterone production at the level of the testis [50]. Repletion of this endocrine deficiency may favor such pathways. Indeed, in a randomized controlled trial treatment in both male and female dialysis patients, supraphysiological dosages of nandrolone for 6 months resulted in a significant increase in lean body mass associated with functional improvement [39]. Moreover, in HD patients, treatment with the androgenic steroid oxymetholone was associated with an increase in fat-free mass, handgrip strength and muscle mRNA levels for several growth factors, together with a decrease in fat mass [53]. Because the combined approach of nandrolone decanoate and RE produced superior anabolic effects [54], long-term studies should be designed to evaluate whether these beneficial effects translate into a survival benefit without serious side effects. Probably, a safer proof of concept is to start by testing the effects on body composition that restoration of manifest testosterone deficiency has in male CKD patients.

**Vitamin D**

Alteration in vitamin D metabolism is more or less ubiquitous in CKD patients and promotes the risk of bone mineral disease [55]. It is less appreciated that deficiency of vitamin D may also promote muscle wasting. Garcia et al. [56] identified key vitamin D-related molecular pathways for muscle regulation and demonstrated that addition of 1,25-vitamin D to myoblasts not only increased expression and nuclear translocation of the vitamin D receptor but also promoted myogenic differentiation by increasing IGF-2 and follistatin expression and decreasing the expression of myostatin [57]. In accordance, a prospective community-based study showed that poor vitamin D status was prospectively associated with greater loss of muscle mass [58]. Moreover, as Sanders et al. [59] showed that vitamin D insufficiency in the elderly was associated with reductions in both bone mineral density and type-2 muscle fibers, a fragile skeleton may in combination with reduced muscle power increase the risk of falls and fracture. Thus, as active vitamin D treatment was associated with increased muscle mass in HD patients [40], vitamin D supplementation should be considered in muscle-wasted CKD patients [55].

**Growth hormone**

GH, IGF-1 and insulin are potent anabolic factors that promote muscle mass gain. Abnormalities in the physiological axis of GH and IGF-1 have been suggested as being important factors in the development of uremic PEW [60]. The GH/IGF-1 axis is controlled by a variety of factors, such as sex, age, ghrelin, exercise, sleep and fat mass [61]. Acquired resistance to the anabolic actions of GH is a potential cause of increased net protein
catabolism in ESRD patients. GH is the major promoter of growth in children and exerts anabolic actions even in adults; protein synthesis, reduced protein degradation, increased fat mobilization and increased gluconeogenesis, with IG-1 being the major mediator of these actions [62]. Evidence suggests that uremia per se and/or the inflammatory milieu is associated with the development of resistance to GH actions at cellular levels [63]. In experimental settings, uremia is characterized by reduced hepatic production of GH-receptor mRNA, as well as reduced hepatic IG-1 mRNA expression [64]. Such cellular biochemical changes would be expected to attenuate the anabolic actions of these hormones [65]. It is interesting to note that similar biochemical abnormalities can also be observed with decreased food intake, and during experimental metabolic acidosis. Metabolic acidosis and decreased dietary protein and energy intake are also associated with decreased IGF-1. Thus, the current evidence suggests an interrelationship between these hormonal, metabolic and nutritional factors, which are involved in the evolution of uremic muscle wasting.

Recombinant human GH administered at pharmacological doses not only improved net muscle protein balance but also improved inflammation, cardiovascular status, lipid profile and erythropoiesis [41, 42]. Beneficial effects of GH on net muscle protein balance are believed to be due to a combination of simultaneous improvements in protein synthesis and protein breakdown. This suggests an involvement of multiple mechanisms, such as direct actions of GH on protein synthesis as well as potential indirect actions through activation of IGF-1. A number of studies have examined whether the long-term administration of anabolic hormones may improve the nutritional status of HD patients with PEW. Trials reported significant increases in lean body mass in the groups that received GH [66, 67] or a super-agonist (AK-0707) that stimulated endogenous GH secretion [68]. Recently, a large GH supplementation trial was prematurely terminated due to logistical reasons. Analysis of completed subjects suggested that rhGH improved a number of risk factors associated with cardiovascular disease risk without adverse outcomes [69]. Currently, rhGH or rhIGF1 is not commonly used to treat muscle wasting in CKD, although these hormones represent a potentially effective intervention in this vulnerable patient population.

**Stimulation of mitochondrial biogenesis**

Mitochondria are the powerhouse of the cells that control cellular metabolism. Recent studies have provided evidence connecting mitochondrial dysfunction (i.e. mitochondria shape, number and function) to muscle loss during periods of disuse [70]. As activators of sirtuins (SIRT), such as resveratrol, were recently shown to ameliorate metabolic disorders and muscle wasting in diabetic rats [71], the hypothesis that sirtuins contribute to better mitochondrial biogenesis via stimulation of the endurance pathway (via activation of PGC-1α) should be considered also in the context of uremia. The expression of PGC-1α is low in dialysis patients [72], and skeletal muscle PGC-1α was recently shown to modulate kynurenine metabolism and mediate resilience to depression in rats [73]. Thus, the links between muscle wasting, low expression of PGC-1α and depression need further consideration in ESRD. Both depression [74] and muscle wasting [75] are exceedingly common in dialysis patients and often occur simultaneously. Further support for testing the therapeutic potential of SIRT1 activators and other exercise mimetics in humans with muscle wasting comes from a recent study showing that SRT2104, a synthetic small-molecule activator of SIRT1, can slow aging and preserve bone and muscle mass in mammals [76]. As SIRT protein blocks the activities of the transcription factors FoxO1 and FoxO3 [77], SIRT1 activation represents an attractive possible novel pharmacological approach to prevent muscle wasting and cachexia [43].

**Myogenic stem (satellite) cells**

The uremic phenotype is characterized by premature aging of especially arteries, bone and muscles [78]. The aging process results from a lifelong accumulation of subtle and/or major damages (such as the toxic uremic milieu) caused by exposure to various biochemical and biological stresses. As we age, skeletal muscle exhibits reduced regenerative potential, impaired myogenic stem cells (called satellite cells) function and decreased satellite cell number. As satellite cells are controlled by both intrinsic and extrinsic regulatory cues and relate to both muscle degenerative disease and sarcopenia [45], novel discoveries in this area may bring new opportunities to enhance muscle function and mass in the uremic milieu. A hallmark of muscular aging is a decreased regenerative capacity after trauma or disease that leads to longer immobilization, sarcopenia and frailty. The ability for muscle to undergo repair is crucial in chronic conditions characterized by muscle wasting. Satellite cells (normally quiescent in the basal lamina) have a remarkable capacity for self-renewal during skeletal muscle growth and repair. It has been estimated that the number of myogenic stem cells decreases with age; from 4–5% at 20–30 years of age to 1% or less at 60–80 years of age [79].

No studies have evaluated the impact of uremia on satellite cells. However, based on studies on the negative impact of uremic toxins on mesenchymal stem cells [80], endothelial progenitor cells [81] and bone marrow-derived stromal cells [82], it can be hypothesized that the toxic uremic milieu will also inhibit the number and function of satellite cells. If satellite cell number and function were inhibited in the uremic milieu, it

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**Potential future treatments for loss of muscle mass in CKD**

The development of effective preventive and therapeutic strategies against muscle wasting is a clinically urgent need in wasting-associated chronic debilitating disorders such as CKD, CHF and cancer. Although a number of new targets for treatment both with regard to inhibition of anabolic signaling and anabolic stimulation have been identified, novel treatment strategies of muscle-wasting disorders have not been approved for treatment in the past decades. Here, we review a few potentially promising novel therapeutic targets (Table 1). The possibility to treat muscle wasting by anti-inflammatory treatment strategies [7, 48] as well as microRNAs [6, 44] has been discussed elsewhere.
would be of interest to study the impact of gene or cell therapy strategies on muscle mass and function. Many different cells, such as myoblasts and CD133+ cells, with myogenic potential have been described [83]. Because nocturnal HD significantly improved the ability of outgrowth endothelial progenitor-like cells to promote angiogenesis and restored perfusion in a model of ischemic vascular disease [84], an impact of dialysis treatment on both number and function of myogenic stem cells could be hypothesized. Moreover, Elabd et al. [85] showed that systemic administration of oxytocin improves muscle regeneration by enhancing activation and proliferation of aged satellite cells. Clearly, such a finding warrants confirmation also in the context of uremia-related muscle wasting.

Manipulation of transforming growth factor (TGF) family members

Myostatin (GDF8) is a member of the TGF-β superfamily and a circulating growth differentiation factor (GDF) that inhibits muscle differentiation and myogenic growth via decreased IGF-1/insulin/Pi3 K/Akt intracellular signaling. As inhibition of myostatin improves satellite cell function, this may be another mechanism through which myostatin may decrease muscle repair by satellite cells. Zhang et al. [46] demonstrated that mice with CKD had 2–3-fold increase in myostatin expression in muscle, that TNF increased myostatin expression (NF-κB-dependent pathway) and that muscle cells exposed to myostatin stimulated IL-6 production. As they also report that myostatin inhibition decreased levels of circulating cytokines, myostatin antagonism might become a therapeutic strategy for improving both muscle growth and decrease of inflammation [86]. Among several interesting options for myostatin inhibition, locally acting proteins that block myostatin, such as activin [87], and proteins that block Stat3 [88] can be mentioned.

Among several cytokines and growth factors that regulate muscle growth and repair, GDF11 has attracted much interest. GDF11 is a circulating factor and member of the TGF superfamily with homology to myostatin. During parabiosis experiments with blood from young mice, GDF11 was shown to reverse age-related cardiac hypertrophy [89] and skeletal muscle regeneration by enhancing activation and proliferation of aged satellite cells. Clearly, such a finding warrants confirmation also in the context of uremia-related muscle wasting.

SUMMARY

Loss of muscle mass (sarcopenia) is a common and ominous feature of the uremic phenotype, especially in dialysis-dependent patients. Because muscle mass normally declines with age, there is a need to establish consensus criteria and compare the prevalence of sarcopenia in CKD with age- and sex-matched controls. As muscle strength may be associated with different risk factors and is a stronger predictor of poor outcome than muscle mass, this opens interesting hypotheses regarding explanatory mechanisms, such as muscular adipose tissue infiltration and increased muscle fibrosis in the uremic milieu. Since established treatment strategies of uremic muscle loss, such as nutritional support, acidosis correction and resistance training, in many cases are insufficient to reestablish muscle mass and strength in this vulnerable patient group, novel treatment strategies are urgently needed. Among a number of potential novel treatment strategies for uremic muscle wasting, stimulation of mitochondrial biogenesis, manipulation of TGF superfamily members, microRNAs and myogenic stem cells holds promise for more effective future treatment of this harbinger of poor quality of life and premature death.

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