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Frailty and Hormones

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> "To the three agencies of frugality, fresh air and no worries we would like to add... the great importance of the functions of the glands with internal secretion as a means of freeing our body from poisonous products, and thus preventing premature old age... on the reinforcement of their functions, if changed by age or disease, by means of extracts obtained from similar organs of healthy animals."
>
> Arnold Lorand
> "Old Age Deferred"—1910

The concept of frailty and its prevention represents a major emerging area in the care of older persons [1,2]. While the frail older person is easily recognized by clinicians, coming to an acceptable definition has been fraught with difficulty. Early definitions focused on qualitative rather than quantitative features of the syndrome. For example:

> "Frailty occurs when there is diminished ability to carry out important practiced social activities of daily living."
>
> Brown et al. [3]

> "Frailty is a random effects model for time variables, where the random effect (frailty) has a multiplicative effect on hazard."
>
> Hougaard et al. [4]

More recently attempts have been made to provide quantitative definitions of frailty. Of these, the definition developed by Linda Fried and her colleagues [5] has emerged as a useful approach for both clinical and research purposes. The elements of the Fried definition of frailty are:

- Weight loss
- Exhaustion
- Weakness (grip strength)
- Slow walking speed
- Low physical activity

Based on this definition, approximately 6.9% of community dwelling older persons are frail. Frailty is present more often in women than men. Frailty is a precursor for functional deterioration, falls and mortality. Functional deterioration is itself a strong predictor of institutionalization and death.

There are many causes of frailty. Of these, alterations in hormones and cytokines represent major factors involved in the pathophysiology of frailty. In addition, persons with diabetes mellitus are particularly prone to develop frailty. Osteoporosis and hip fracture are commonly associated with frailty. Thus, with the aging of the population, frailty is becoming a condition of major interest to endocrinologists.

Hormones and Frailty

Testosterone

It is now well accepted that total testosterone declines at the rate of approximately 1% per year in males as they age [6,7]. Because of the increase in sex hormone binding globulin, free and bioavailable testosterone decline at an even greater rate [8]. This fall in testosterone with aging is associated with a decline in muscle mass and strength, bone mineral density and cognition [9–11]. In addition, a number of symptoms of frailty such as fatigue are associated with low testosterone levels.

Testosterone replacement studies have demonstrated a clear increase in muscle mass in males [12–14] and in persons who are truly hypogonadal an increase in muscle strength [15,16]. Low testosterone levels are associated with hip fracture [17]. Testosterone replacement has been shown to improve cognition in animals and in some human studies [18–20].

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Low testosterone levels are associated with poor function in older persons [21]. Testosterone replacement in patients following hospitalization has resulted in improvement in function [22,23].

Overall, there is a reasonable body of evidence that low testosterone plays a role in the development of frailty in males [24,25]. In females, testosterone levels decline rapidly from 20 to 40 years of age [26]. Testosterone replacement has been shown to increase muscle mass and bone mineral density. With the availability of a testosterone patch for females in the United States, there will be a marked increase in the enthusiasm for the use of testosterone to attempt to prevent frailty in older females.

Dehydroepiandrosterone (DHEA)

DHEA and its sulfate decline rapidly with aging [27,28]. The role of DHEA, other than as a precursor for sex hormones remains uncertain. High doses of DHEA (100 mg/day) improved muscle strength in males [29]. However, a year-long study of 50 mg/day of DHEA in older males and females was disappointing in that it produced minimal effects [30,31]. DHEA cannot be recommended at present for the prevention and/or reversal of frailty.

Vitamin D

$25(OH)_2$ Vitamin D has been shown to decline with aging in a longitudinal study [32]. Calcium and vitamin D play a key role in the prevention of fracture in nursing home residents [33] and in elderly community dwelling residents [34]. Some, but not all studies, suggest that vitamin D levels correlate with muscle mass and strength [35–38]. In addition, the vitamin D receptor translation start site (FoKI) is significantly associated with sarcopenia in older males [39]. Low levels of vitamin D, but not normal levels, are associated with falls and functional decline [40,41]. Vitamin D replacement in persons who are vitamin D deficient reverses these deficits only in older persons with low vitamin D levels [42].

Growth hormone and insulin growth factor-I (IGF-1)

Dan Rudman [43] suggested that older persons underwent a growth hormone menopause. However, replacement of growth hormone in older persons has failed to produce any positive effects in frail elderly and has been associated with multiple side-effects [44–46]. Short-term use of growth hormone in malnourished older persons does appear to have the potential to reverse the malnutrition and improve functional status [47,48].

Skeletal muscle is responsible for the production of 25% of circulating insulin growth factor-1 (IGF-1). There are two muscle isoforms. One is similar to liver IGF-1, the other has a different 3'ex on sequence (mechano-growth factor) and has local actions on muscle [49]. It is termed IGF-IEc. Exercise (stretch) leads to upregulation of the mRNA for both muscle isoforms. Reduced muscle IGF-1 signaling leads to muscle atrophy. Muscle IGF-1 is controlled by hormones (growth hormone, testosterone, insulin and vitamin D) and muscle exercise [50]. Corticosteroids, cyclosporine and TNF-alpha can inhibit the production of muscle IGF-1. IGF-1 enhances muscle growth partially by increasing satellite cell production [51]. IGF-IEc also stimulates protein synthesis in muscle [52]. Electroporation of IGF-1 stimulates muscle fiber hypertrophy [53]. A localized IGF-IEc transgene prevented age-related muscle atrophy and allowed older animals to develop a similar proliferative response to muscle injury as that seen in younger animals [54].

Thyroid

There is evidence that with aging there is a decline in the ability of thyroid hormone to fully activate its receptor [55]. However, there is little evidence that thyroid hormone effects associated with the physiological changes of aging play a role in the pathogenesis of frailty. Hypo- and hyperthyroidism are associated with a decline in muscle strength and cognitive dysfunction and thus can produce frailty [56]. Apathetic thyrotoxicosis needs to be considered as a cause of rapid onset frailty.

Cortisol

Cortisol levels are either unchanged or increase slightly with aging [57]. Like thyroid hormones, cortisol does not appear to play a role in frailty. On the other hand, cortisol deficiency (Addison's disease) is not a rare condition in older persons. It presents with abdominal complaints, diarrhea, fatigue, muscle weakness and weight loss. This constellation of symptoms with a low potassium, borderline high sodium and eosinophilia should raise suspicion of Addison's disease.

Diabetes Mellitus

Diabetes mellitus occurs in up to 20% of older persons [58]. Numerous studies have found that persons with diabetes mellitus have greater functional decline than other older persons [59–64]. Persons with diabetes are much less likely to read, garden, use the telephone, write letters or go out socially [65]. Diabetics have an increase in injurious falls. Longterm mobility and resistive training improves mobility and strength in older diabetics [66].

The reason(s) for increased frailty in older diabetics is multifactorial [67]. Neuropathy leads to decreased balance and a decline in muscular function. Peripheral vascular disease leads to a decline in muscle mass in the lower

extremities. In addition, diabetics develop accelerated cognitive decline. However, this alone does not produce frailty, as many humans with dementia are not frail until the terminal stages of the disease. Moreover, the SAMP8 rodent model of excess amyloid beta protein production and premature memory problems shows no evidence of frailty [68–70]. Hyperglycemia produces a decrease in the ability to learn and in memory both in rodents and humans [71–73]. Returning glucose levels to normal reverses these cognitive problems [74]. Diabetics have an increase in vascular lesions in the central nervous system leading to cognitive decline [75]. Recently, it has been suggested that hyperinsulinemia may accelerate the development of Alzheimer's disease [76–78]. This is due to the fact that insulin degrading enzyme also degrades amyloid beta protein. Hypertriglyceridemia is common in diabetics and is associated with cognitive dysfunction [79]. Lowering triglyceride levels with gemfibrozil enhances cognition [80]. Hypertriglyceridemia produces leptin resistance at the level of the blood brain barrier [81]. Leptin enhances long term potentiation in the hippocampus, suggesting that it plays a role in memory functioning [82].

Cytokine Related Aging Process

Increased release of cytokines with aging appears to play a role in the physiological aging process [83]. C-reactive protein, a non-specific marker of cytokine release, is associated with declines in function and increased mortality [84–86]. Cytokines also impair cognition by crossing the blood brain barrier [87].

Interleukin-6 is released from lymphocytes and macrophages and has been characterized as the geriatric cytokine [88]. IL-6 levels increase with aging and down-regulate tumor necrosis factor α (TNF) and interleukin-1 (IL-1). IL-6 is associated with osteoporosis and with loss of muscle mass [89–91]. It also produces activation of the hypothalamic-pituitary-adrenal axis, fever, activation of the hepatic acute phase response and hemodilation [92]. IL-6 is produced by osteoclasts. It activates osteoclastic activity and bone resorption [93]. IL-6 production from osteoclasts is increased by parathyroidhormone [94]. IL-6 is a strong predictor of disability.

Tumor necrosis factor alpha is a proinflammatory cytokine that produces anorexia and lipolysis [83]. It is a myocardial depressant which induces apoptosis in heart myocytes. It is associated with insulin resistance and mediates the receptor activator of NF-Kappa β ligand (RANKL)-induced osteoclastic differentiation [95,96].

Anemia is a marker for frailty [97,98]. TNFα, IL-1 and IL-6 inhibit erythropoietin production and inhibit the committed progenitor from multipotential stem cells converting to an erythrocyte by increasing apoptosis [83].

The Health ABC study showed that TNFα and IL-6 were related to smaller muscle area, less appendicular mass, lower knee extensor strength and less grip strength [99]. Another study found that physical performance score declined with high levels of CRP and interleukin-6 [100]. Overall, these studies strongly support the concept that the Cytokine Related Aging Process is a precursor for frailty [83].

Weight Loss and Frailty

Weight loss is a hallmark of the frailty syndrome [101]. There are four major causes of weight loss. These are starvation (anorexia), sarcopenia, cachexia and dehydration.

Dehydration

Dehydration occurs in approximately 10% of older persons who are losing weight. Physicians have classically used a blood urea nitrogen to creatinine ratio of greater than 20:1 to define dehydration. In older persons this is a poor measure because of the increased renal failure, congestive heart failure and gastrointestinal bleeding. In older persons, osmolality must be measured to confirm the presence of dehydration.

Older persons fail to recognize thirst due to a failure of the mu opioid drinking drive [102]. This puts older persons at increased risk for developing dehydration when they have increased insensible fluid loss during fevers or are given diuretics. In addition to an increased risk in developing dehydration, older persons also are at increased risk of developing hyponatremia [103]. This appears to be predominantly due to the altered effects of arginine vasopressin on aquaphorin in the collecting tubule cells.

Starvation

While occasionally poverty results in true starvation in older persons, most fail to ingest adequate calories because of anorexia [104]. With aging there is a physiological anorexia that occurs to offset the decline in physical activity with aging [105]. Males have a greater physiological anorexia than do females. Changes in taste, smell and dentition play a small role in the pathophysiology of this anorexia. A major reason for the physiological anorexia is an alteration in the ability of the stomach to handle large caloric (>500 calorie) loads [106]. There is a decrease in fundal compliance with aging, which leads to a more rapid antral filling and therefore, early satiation [107,108]. The decrease in fundal compliance is due to a decline in nitric oxide generation in the fundus in response to food stimuli [109].

There is an increase in basal and circulating cholecystokinin (CCK) in older persons in response to fat in

the duodenum [110]. CCK is a satiating hormone. The increase in CCK is due to a decreased clearance [111]. CCK also has greater satiation effects in older, compared to younger persons.

The decline in testosterone in older males leads to an increase in leptin levels [112]. Leptin has anorectic effects [113]. Replacement of testosterone leads to a fall in leptin levels [16].

Nitric oxide is a major mediator of peptide effects on appetite within the central nervous system [113,114]. Animal studies suggest that nitric oxide synthase levels in the hypothalamus decline with aging [115]. This suggests that nitric oxide may be the final common pathway for mediating the anorexia of aging.

Social isolation represents a major cause of anorexia in older persons. Providing companionship during meals represents a simple intervention that decreases nutritional risk [116].

Depression is the most common treatable disease that causes anorexia and weight loss in older persons [117–119]. In one-third of older persons depression is the major cause of weight loss and weight loss is reversible with adequate treatment of depression. Cancer accounts for approximately 10% of the weight loss. Therapeutic diets, such as the American Diabetic Association diet, are a major cause of pathological weight loss in nursing home residents and are no longer recommended in institutionalized elders [120].

Sarcopenia

Sarcopenia is the loss of muscle mass with the aging process [121–123]. As has already been pointed out, it is strongly related to the loss of hormones, such as testosterone and IGF-1, and to mild increases in cytokines. Other causes of sarcopenia include diminished neuronal input into muscle, decreased food intake (particularly protein and creatine), and peripheral vascular disease [124]. In a longitudinal study it was shown that persons who have lost muscle mass, but remain obese (sarcopenic obesity), have an extremely high rate of future disability and death.

Myostatin plays a key role in inhibiting muscle protein synthesis [125]. Mice with a deletion of the myostation gene have increased musculature [126]. A young boy with a double deletion of the myostatin gene developed extraordinary musculature in the first year of his life [127]. Transgenic mice with the myostatin gene develop severe muscle wasting [128]. While the role of the myostatin gene in the pathogenesis of sarcopenia has not been determined, it appears to have great potential for enhancing our understanding of sarcopenia.

Cachexia

Cachexia occurs in the face of illness when there is a marked excess secretion of cytokines such as tumor necrosis factorα, interleukin-1 and interleukin-6 [129]. These cytokines activate the ubiquitin-proteasome syndrome resulting in proteolysis and inhibit NF Kappa $\exists$ to reduce protein synthesis. Cytokines also produce insulin resistance, inhibit hepatic lipoprotein lipase, produce lipolysis,

Table 1. *Factors involved in the pathophysiology of frailty*

Sarcopenia

- Hypogonadism
- Low vitamin D
- Decreased Insulin Growth Factor-I
- Cytokines (IL-1,IL-2,TNF α)
- Vascular disease
- Decreased food intake
- Decreased innervation of muscle
- Decreased physical activity
- ? Myostatin

Weight Loss

- Dehydration
- Physiological anorexia
  - Decreased taste and smell
  - Decreased fundal compliance
  - Increased cholecystokinin
  - ? Decreased ghrelin
  - Increased leptin in males
- Pathological anorexia
  - Depression
  - Medications
  - Metabolic conditions
  - Nosocomial infections
  - Dysphagia
  - Therapeutic diets
- Cachexia
  - Marked cytokine excess associated with cancer, chronic obstructive Pulmonary disease, renal disease, cardiac failure, tuberculosis, etc.

Psychological factors

- Depression
- Anxiety (e.g., fear of falling)
- Mild cognitive impairment
- Dementia
- Social isolation

Impairment of vision and hearing

Vascular Disease

- Diabetes mellitus
- Chronic heart failure
- Peripheral vascular disease
- Vascular dementia

Hip fracture

- Inadequate exercise
- Inadequate calcium ingestion
- Inadequate vitamin D
- Genetics

decrease intestinal mobility, lower circulating albumin levels and result in anorexia and sickness behavior.

Both testosterone and progestagens, such as megestrol acetate, can inhibit cytokines [130,131]. Megestrol acetate is a glucocorticoid progestational agent, having about double the glucocorticoid effect of cortisol *in vitro* [132]. Thus, the decline in the stimulable levels of cortisol in persons receiving megestrol acetate is an expected effect, similar to that seen with prednisone. Megestrol acetate has been shown to enhance appetite, increase weight and improve quality of life in a systematic literature review of patients with cancer [133]. Megestrol acetate increased weight and albumin in older persons with weight loss [134,135]. This effect was correlated with the level of circulating cytokines [136]. Megestrol acetate also enhanced weight gain in patients with chronic obstructive pulmonary disease in a double-blind multi-center trial [137]. Of interest is that megestrol acetate produced weight gain despite its ability to decrease testosterone [138].

Conclusion

Numerous factors are involved in the pathophysiology of frailty (Table 1). Among these factors, low testosterone in males, low IGF-1 and elevated cytokines appear to be key regulators of the frailty process. Dementia alone does not produce frailty. Older persons with diabetes mellitus are particularly prone to become frail for a multitude of reasons. Weight loss is a hallmark of the frailty syndrome. Persons with frailty are at increased risk for functional decline and early death.

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