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Review

The aging population – Is there a role for endocrine interventions?

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Abstract

The expected increase in the aging population will have a significant impact on society and the health system in the coming years and decades. Enhancing healthspan, "healthy aging", and thus extending the time that the elderly are able to function independently is a significant task and is imperative. Age-dependent changes such as weight loss, sarcopenia and anorexia, which contribute to the development of frailty in the elderly are discussed. The role of the age-dependent decrease in growth hormone secretion in this process and the potential benefits and risks of hormonal interventions to delay, prevent or reverse frailty in the elderly are reviewed.

Keywords: Aging; Healthspan; Frailty; Growth hormone

1. The aging population, demographic data

In the developed world, people over the age of 80 years are the fastest growing subset of the population [1]. In the United States alone, the proportion of the population over the age of 65 years is expected to increase from 35 million (12.4%) in 2000 to 71 million (19.4%) in 2030, and the number of persons aged >80 years is projected to increase from 9.3 million in 2000 to 19.5 million in 2030 [2]. The worldwide population aged >65 years is projected to increase between 2000 and 2030 from 420 million to 973 million. The largest increase in absolute numbers will occur in the developing countries where the population over the age of 65 years will increase from about 249 million in 2000 to an estimated 690 million in 2030 [3]. Michel et al. [4] suggest by the year 2050 individuals aged 60 years and older will represent 25% of the world's population and 75% of the group aged >80 years of age will live in the developing world. About 7 million Americans over the age of 65 years depend on others for help with some basic task of daily living [5]. Third national health and nutrition examination survey (NHANES III) data show that 23% of people aged 80 years and older are unable to prepare their own meals and 17% are unable to walk. Complications resulting from falls are the sixth leading cause for death in people over 65 [6]. Some estimates suggest that by 2050 there will be more than 4.5 million hip fractures annually compared to a total of 1.26 million hip fractures in 1990 [7]. Depending on the underlying assumptions this number could increase to up to 21.3 million annually [7]. Currently the chances of dying without disability at age 80 years and older is less than 25%, even for those who are still fully independent at age 65 years [8]. Frailty increases with advancing age and is associated with a high risk for mortality, institutionalization, falls, and hospitalization [9]. Frail older

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adults are less able to tolerate the stress of medical illness, hospitalization, and immobility [9]. Strategies to prevent and/or slow the development of physical frailty will become increasingly important in the next decades in order to keep a greater proportion of the elderly population independent for a longer time. In order to be able to develop such strategies it will be important to explore at what age such interventions should be applied and how their efficacy can be measured. Also the cost of the intervention strategies in terms of adverse or negative effects on the individual will need to be assessed. This will require not only scientific but also ethical, cultural, social and economic considerations. The following discussion will focus on frailty (unrelated to disease) and conditions, which contribute to its development, such as: weight loss, sarcopenia, anorexia of aging and cachexia. The central hypothesis, which is the basis for the discussion, is that the age dependent decrease in growth hormone secretion from its peak at mid puberty is responsible for the changes of body composition seen with aging and are contributing to the development of frailty. We will discuss whether there is a role for hormonal interventions in the prevention and/or modification of these age-related changes.

2. Definitions of frailty

Frailty is a progressive, physiologic decline of multiple body systems which is characterized by loss of function, loss of physiologic reserve and increased susceptibility to acute illness, falls, disability, institutionalization and death [10,11]. While frailty is more prevalent in patients with multiple diseases, it also can be present without disease and possibly represents an independent physiologic process [11].

Several different definitions of frailty have been published and most of them are synonymous with disability, comorbidity or advanced old age. While they differ in their conceptual approach, the majority of researchers are in agreement that frailty is a definable clinical state. The definitions range from using a phenotype [10,12] to methods that consider deficit accumulation [13–16]. Some definitions include declines in mobility, strength, endurance, nutrition, and physical activity [17,18,10] and others include cognitive impairment and depression [18–20]. One of the most widely used definitions has been presented by Fried et al. [10], which used data from the Cardiovascular Health Study. Frailty is defined as a clinical syndrome using a 5-item phenotype definition, in which 3 or more of the following criteria are present (intermediate or prefrail: one or two criteria present): unintentional weight loss (>10 lbs (4.5 kg) in past year), self-reported exhaustion (modified 10 item center for epidemiological studies-depression scale (CES-D))[21], weakness (grip strength in the lowest 20% adjusted for gender and BMI), slow walking speed (lowest 20% based on time to walk 15-feet, adjusted for gender and standing height) and low physical activity (lowest quintile of kilocalories expended per week). The authors [10] show that this standardized phenotype of frailty has predictive validity for falls, hospitalizations, disability and death in the elderly. These findings persisted after adjusting for health status and disability at baseline, suggesting that frailty can be distinguished from disability or disease [11].

Physiologic correlates which result in "physiologic" frailty, include sarcopenia, anorexia, cachexia, decrease in hormones. One of the main clinical symptoms of frailty is unintentional weight loss [22] (see Fig. 1).

3. Weight loss in the elderly

Weight loss is the main indicator of frailty in older people [22]. The main causes of weight loss in the

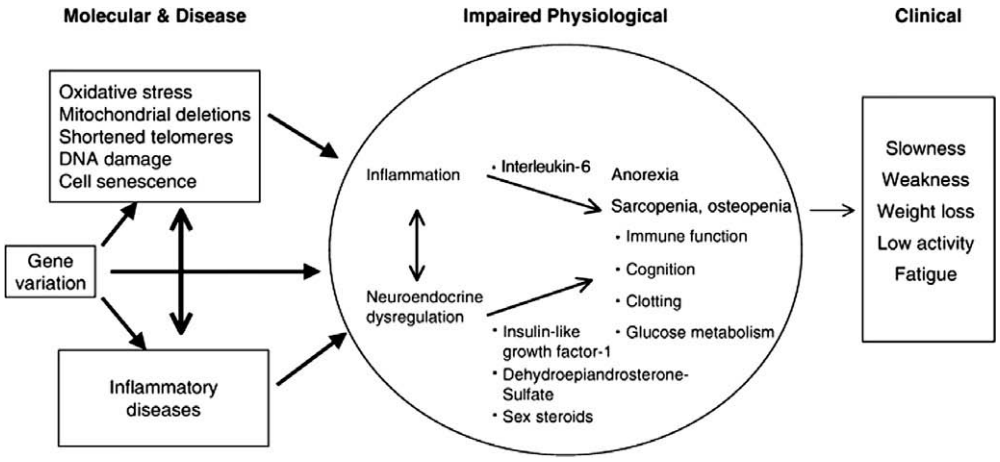

Fig. 1. Overview of molecular, physiological and clinical pathway to frailty. (Reproduced by the kind permission of The American geriatric society, [22]).

elderly include cachexia, anorexia and sarcopenia. Involuntary weight loss in people over 60 years of age is predictive of mortality [23,24] and leads to frailty. In addition while fat mass increases in middle age, it declines beyond 70 years of age [25]. The NHANES III found the prevalence of obesity in the 70–79-year age group to be 20% in men and 25% in women, while in those over 80 years old the prevalence was only 8% in men and 15% in women [26]. Nursing home residents who have continued weight loss have a 30% chance of death in the following 6 months, while in those who regain the weight the likelihood of dying is reduced to 10% [27]. Several studies suggest a relationship between low BMI (kg/m^2) and increased death rate in the elderly. Thomas et al. [28] shows that in the older population a BMI of less than 20 together with a decrease in activities of daily living (ADL) predict poor outcome in hospitalized patients. At a BMI of less than 20.5 in men >75 years of age, a 20% higher mortality risk is observed, while in women >75 years a 40% higher mortality risk is observed [29]. In patients with Alzheimer's disease, weight loss also has been found to be a predictor of mortality. In a 4-year study of community-dwelling older adults, unintentional weight loss was associated with a greater rate of functional decline [30].

4. Cachexia

Cachexia can be described as cytokine-associated wasting of protein and energy stores [31]. Some of the diagnostic criteria for cachexia found in the literature include: unintentional weight loss (>5%), BMI <20 under age 65 years and BMI <22 age 65 years and older, albumin <35 g/L, low fat-free mass (lowest 10%) and evidence of cytokine excess (e.g. elevated C-reactive protein) [32]. Cachexia is associated with many conditions such as cancer, heart failure, AIDS [33,34] and it is also considered to be partially responsible for the weight loss in the elderly, independent of the anorexia of aging. Cachexia is associated with an almost equal loss in fat and muscle mass whereas in starvation the loss is initially greater for fat than muscle tissue [31]. The underlying pathophysiology is not fully understood and cytokines, as well as proinflammatory cytokines appear to play a role [32,35]. Besides the C-reactive protein, interleukin 6 (IL-6) has been found to be elevated in community-dwelling frail older adults [36,37] and it was found to be associated with sarcopenia and weight loss [38]. High IL-6 concentrations together with low IGF-I levels in a cohort of community-dwelling older women were associated with a high risk for progressive disability and death. This effect was additive [39] indicating an independent effect of IL-6.

5. Anorexia

There is a physiological reduction in appetite and food intake in the healthy elderly which has been termed the anorexia of aging [40]. According to the NHANES III data [41,42], the energy intake between the ages of 25 and 70 years can decline by up to 1000–1200 kcal/day for men and 600–800 kcal/day for women. At age 80, 10% of men consume less than 890 kcal/day and the same percentage of women consume less than 750 kcal/day. The significance of this phenomenon is underscored by the finding that in older people anorexia independently predicts mortality [43].

Reasons for the development of the anorexia of aging include decline or loss of olfaction, changes in oral health, increase in some taste thresholds [44] as well as a decreased rate of stomach emptying and an increased release of the satiating hormone cholecystokinin [45,46]. The later seems to be due to an age-dependent decrease in the clearance of cholecystokinin. [47]. Other gut hormones which might play a role in the anorexia of aging, include GLP-1 and polypeptide YY. Both are thought to decrease appetite but their role in the anorexia of aging remains unclear. In support of a role for GLP-1 are the results of Ranganath et al. [48] who found significantly higher concentrations of GLP-1 in response to a 100-g oral carbohydrate load in postmenopausal women when compared to premenopausal women. MacIntosh et al. [49] could not find such an association. While the increase of these factors associated with intraduodenal fat infusion was significantly correlated with a decrease in hunger in young adults, such a correlation could not be found in the elderly. Similarly there is no evidence supporting a causative role for PYY in the development of the anorexia of aging [50].

6. Sarcopenia

Sarcopenia is recognized as a major contributing component of the multi-systemic decline leading to frailty [22]. The estimated average muscle loss per decade is between 1% and 5% after the age of 40 years [51,52]. Forbes et al. [53] describe a linear loss of about 12 kg between age 25 and 65 years in men when using K^{40} counting to quantify changes in lean body mass. Women showed a decline of 5 kg over the same time period. These findings suggest that the age-associated decline in men is significantly steeper than in women, a finding supported by the data of Janssen et al. [54].

The term sarcopenia in humans describes the loss of muscle protein mass, function and muscle quality that accompanies advancing age. Sarcopenia differs from acute atrophy caused by disuse in several ways: while disuse causes a reduction in muscle mass with preserved fiber number and specific force, in sarcopenia fiber num-

ber and specific force are reduced and there is a shift toward expression of slow fiber types. This shift to a relatively higher proportion of type I fibers with aging occurs independent of rigorous endurance exercise [55].

No clear criteria have been established for defining sarcopenia in clinical studies or in daily clinical practice. While some studies have used a definition based on measuring muscle mass, others have included measures of muscle strength. The rationale for the latter is based on data showing that muscle strength is independently related to lower extremity performance [56]. Thus a discrepancy exists between muscle mass and the amount of force generated by the muscles and this discrepancy tends to increase with age. One possible explanation is the increase in muscle fat infiltration with age [57].

Different methods have been used to assess loss of muscle mass in epidemiologic studies, such as dual-energy X-ray (DXA), bioelectrical impedance (BIA), as well as predictive equations using anthropometric measures together with grip strength. Many studies use the cut off of $\leqslant 2$ standard deviations when compared to a young adult population. Baumgartner et al. [58] and Melton et al. [59] define sarcopenia as a height-adjusted appendicular muscle mass of two or more standard deviations below the mean of young adults. Janssen et al. [60] using BIA measurements, used muscle mass relative to body weight expressed as skeletal muscle mass index (SMI) to define sarcopenia. Class I sarcopenia was defined as a SMI between -1 to -2 standard deviations and class II sarcopenia was defined as a SMI $\leqslant 2$ standard deviations of young adults [60]. In this study [60] the relationship between sarcopenia and functional impairment was analyzed in 4504 adults aged 60 years and older using data of the NHANES III. The likelihood of functional impairment and physical disability was 2-fold greater in older men and 3-fold greater in older women with class II sarcopenia. When skeletal muscle mass relative to body weight was 30% below the mean of young adults, an increased risk of functional impairment and disability was observed. Baumgartner et al. studied 808 older non-Hispanic caucasians and Mexican–American men and women [58]. They reported that sarcopenia is independently associated with disability and a history of falling. Melton et al. [59] show an association between sarcopenia and an increase in fractures in older men and women. Other studies have attempted to find early markers of sarcopenia that could be used as predictors of physical limitations in the elderly. Janssen et al. [61] describe skeletal muscle mass criteria, which are associated with higher likelihood for developing physical disability. Their findings demonstrate that the likelihood of physical disability is increased to a high degree when SMI values were $<5.75\ kg/m^2$ in women and $<8.50\ kg/m^2$ in men. Lauretani et al. [62] using criteria of isometric muscle strength, muscle power and muscle cross-sectional area, find that knee extension torque, hand grip strength and lower extremity muscle power have similar discriminating value in identification of poor mobility, favoring hand grip strength measurement as a screening measure for sarcopenia.

Overall, the published literature suggests that the age-dependent loss of muscle mass (sarcopenia) and function is linked to physical frailty and decreased capacity of independent living. Independent of which definition is used for sarcopenia, the prevalence of sarcopenia increases with age.

The data on the etiology of the age-dependent muscle loss include a wide variety of factors such as the loss of alpha-motor neurons [63], the reduction in dietary protein [64], a decreased level of physical activity [65] as well as an increase in catabolic cytokines such as interleukin-6 [66] and TNF-alpha, Il-15 and CNTF (ciliary neutrophobic factor) [67]. The CNTF-induced cachectic effects were shown in mice implanted with C6 glioma cells, which were genetically modified to secrete CNTF [68].

Marzetti et al. [69] describe that at a cellular level sarcopenia is caused by an age-dependent acceleration of myocyte loss through apoptosis. Quantitative and qualitative changes in Ca^{2+} and K^{+} ion channels are also involved in the age-related decline in muscle force [68,70]. The decrease in steroid hormones and growth hormone are also possibly involved in the age-dependent decrease in muscle mass [71] as well as age-related vitamin D deficiency [68]. K^{+} channels are essential to induce myogenesis and proliferation of muscle cells and are modulated by IGF-I [73]. Overexpression of IGF-I in skeletal muscle increases the number and prevents the age-related decline in voltage gated L-type Ca^{2+} [67]. Mechano growth factor (MGF), a splice variant of IGF-I, acts locally as an autocrine/paracrine factor, and is involved in the activation of muscle stem (satellite) cells. In elderly men, compared to the young, there is an age-dependent reduction in the MGF response to acute resistance training [74], which helps to explain the age-dependent muscle loss.

7. Interventions

The treatment spectrum of progressive frailty in the elderly, includes the broad range from symptom relief to hospice care [11]. So far hormonal interventions in the elderly have shown improvements in body composition but not in function. Theoretically, in order to be effective, hormonal interventions need to be implemented early in the process of developing frailty. We discuss GH, steroid, ghrelin mimetic and Vitamin D replacement therapy as well as beneficial effects of exercise in the elderly.

7.1. GH therapy in the elderly

Several age-dependent changes in body composition [75–77] such as muscle loss have been associated with the age-dependent decline in GH in humans [78]. Circulating GH levels show a significant decline with aging. In elderly subjects, the 24-h integrated GH concentration is in the same range as levels observed in young patients with GH deficiency [79]. Several authors have described a reduction in GH secretory parameters from 15% to 70% in men and women over 60 years of age when compared to young adults [80]. Growth hormone levels decrease by 50% every 7 years after midpuberty [81]. Therefore, it is no surprise that the use of GH as an anti-aging therapy ranks as number 1 of the health-related internet searches [82]. Annual off-label use for GH for its anti-aging effects is conservatively estimated at US $100 million dollars.

Despite the attention that GH therapy has received as a potential anti-aging treatment option, there are only few proven beneficial effects of GH therapy in the older population. GH therapy in the elderly is able to increase IGF-I levels by 88% in the GH-treated patients, compared to only 2% in patients treated with placebo. On average, GH therapy in the elderly has been shown to reduce fat mass by 2.08 kg and more importantly it increases lean body mass on average by 2.13 kg. Overall there has been a reported decrease in total cholesterol with GH therapy [82].

The expectation that GH treatment might have beneficial effects in the elderly was based on study results in patients with adult- or childhood-onset GH deficiency [83–86]. One of the hallmarks of frailty is the loss of muscle mass and one of the most consistent beneficial effects described with GH treatment in patients with adulthood as well as childhood onset GH deficiency, is the increase in lean body mass [83,86,87]. GH stimulates skeletal muscle protein synthesis [88,89] and possibly inhibits protein degradation via stimulation of IGF-I [90,91].

Despite these beneficial changes in lean body mass [82], none of the studies conducted in the elderly have shown a beneficial effect of GH treatment on function, strength or quality of life parameters [92]. The only study which could demonstrate a marginal beneficial effect of GH treatment on strength in the elderly was published by Blackman et al. [93], when GH was given in combination with testosterone. The shortcoming in finding beneficial effects in function or strength in the studies published to date may be explained by difficulties associated with designing geriatric studies and by the relatively short term administration of the replacement therapy, while the process of aging is slow and progressive.

The side effects of GH therapy in the elderly are similar to the side effects found in young adults. The main side effects included soft tissue edema (50%), arthralgia (21%), carpal tunnel syndrome (19%) and gynecomastia (5%). Of note, there was also an increase in impaired glucose regulation (22%) and new-onset diabetes (5%) in the elderly treated with GH [78]. It should be noted that the dose of GH required to increase IGF-I levels to young adult values is lower as the subject ages, suggesting that tissue sensitivity to GH increases with age. Thus in patients (not on oral estrogens) over the age of 60 years of age a dose as low as 0.1 or 0.2 mg/day is required while in a twenty year old it might be as high as 0.5 mg/day.

A serious concern about GH therapy in the elderly relates to the potentially increased risk for developing cancer or leading to cancer progression. *In vitro* data show that GH/IGF-I provides an anti-apoptotic environment, with IGF-I having powerful proliferative effects in almost all tissues. These could favor the survival of genetically damaged cells and as a consequence of this increase the risk for developing cancer. This concern is particularly relevant in the older population since there is a greater likelihood of the presence of such cells. Long-term data in children and adults with GH deficiency treated with GH for 27,000 patient-years have shown no increased overall occurrence of *de novo* neoplasia or of re-growth of primary pituitary tumors [84,94]. A review of the current data suggests that GH replacement therapy in GH deficient adults is safe and does not lead to tumor formation [95,96]. However, these are in individuals who are GH deficient and receive GH as a replacement therapy. This is not identical to the elderly where GH is being given to restore 'youthful' levels whereas in the GH deficient state, it is designed to restore age appropriate levels. Therefore, currently available safety data from surveillance studies in GH deficient patients do not allow the conclusion that GH is safe to give long-term to the healthy elderly.

7.2. Ghrelin-mimetic therapy in the elderly

Ghrelin mediates several effects which could be potentially beneficial for the older population. Besides increasing GH and IGF-I levels, it also has orexigenic effects [97,98]. The GH response after activation of the GHSR1a receptor is similar in young and old adults [99] and the pituitary GHSR1a receptor content does not decline with age [100]. Orally active ghrelin-mimetics are available [101,102] and they have potentially beneficial effects in catabolic conditions [103]. In rodents, treatment with an orally active ghrelin-mimetic showed an increase in weight and food intake and protected the animals from chemotherapy induced weight loss [104]. Chronic cytokine elevation has been shown to be associated with the cachexia of aging [105] and Cappola et al. [39] found that the combination of low IGF-I and high IL-6 levels confer a high risk for progressive

disability and death in older women. Ghrelin treatment of rodents has been shown to reduce LPS-induced chronic production of pro-inflammatory cytokines such as IL-6, TNF-alpha and IL-1beta [106]; an effect which is thought to be mediated through the GHSR1a receptor. Similarly, ghrelin-mimetics have been shown to increase food intake and weight in normal healthy young adults as well as fat free mass [107,108]. In a 1-year placebo-controlled study in healthy older adults over the age of 60 years, with an oral ghrelin-mimetic (MK-677), an increase in appetite was observed. The GH/IGF-I axis was restored into the normal range for young adults and the increase in GH and IGF-I was associated with an increase in fat free mass [109]. The current studies in the elderly, have not shown a significant increase in strength or function in the ghrelin-mimetic treatment group, when compared to the placebo group, however a tendency was observed [110].

A concern of the use of these compounds, includes the potential deterioration of insulin sensitivity and development of diabetes mellitus in older adults with impaired glucose tolerance [111].

7.3. Testosterone therapy

Serum testosterone levels decline significantly with aging [112]. Testosterone increases muscle protein synthesis [113] and the effects of testosterone on the muscle are modulated by several factors including genetic background, nutrition and exercise [114]. Hypogonadal men have increased percent body fat [115]. Studies of young, hypogonadal men have reported a decrease in fat mass with testosterone replacement [116], whereas others did not find a change [117]. Up to 20% of men with vertebral fractures and 50% of men with hip fractures have biochemical evidence of hypogonadism [118,119]. Two meta analyses suggest that testosterone therapy increases lumbar bone density in men after 12–36 months of treatment [120,121]. A meta analysis of 11 randomized trials by Ottenbacher et al. [122] suggests that testosterone/DHT therapy in older men increases muscle strength, however the mean was influenced by the results of one study. Giannoulis et al. [123] describe an increase in midthigh muscle area, an increase in one of six measures of muscle strength and an increase in aerobic capacity in a 6 months randomized clinical trial with GH and testosterone in a group of 80 healthy older men ages 65–80 years.

In a large randomized, double-blind, placebo-controlled, short-term study (6 months) with 207 healthy older men (age 60–80 years) with low normal testosterone levels, testosterone supplementation increased lean body mass and decreased fat mass without accompanying changes in functional mobility, strength or quality of life measures [124]. No change in bone mineral density was found. A longer study might have been necessary in order to be able to detect changes in bone density. Of concern was the observed decrease in HDL cholesterol levels.

7.4. Vitamin D therapy

In the elderly, serum levels of vitamin D fall significantly [68]. Similarly there is an age-dependent reduction in the vitamin D receptor expression in skeletal muscle [125]. The genomic effect of vitamin D in muscle includes changes which have an effect on *de novo* protein synthesis and data from vitamin D knock out mice suggest that it is involved in muscle development and growth [126,127]. Prolonged vitamin D deficiency has been associated with severe muscle weakness, which improves with vitamin D supplementation in humans [72]. Muscle biopsies from patients with osteomalacia show atrophy of the type II muscle fibers which is similar to the histopathological muscle changes found in the elderly [128]. Studies assessing the effect of vitamin D supplementation on fall prevention have shown mixed results. Two studies in a large number of elderly healthy women with severe vitamin D deficiency found a reduction in the number of falls [129,130] in their study population. A long-term placebo-controlled study over 3 years in healthy elderly age 65 years and older with high serum levels of 25(OH) D, did not find a reduction in falls after treatment with vitamin D and calcium [131]. Latham et al. [132] investigating the effects of vitamin D in 243 hospitalized frail older patients did not find an effect on muscle strength, walking velocity or new falls over a period of 6 months.

The "extra bone" effects of vitamin D provide a rationale for the supplementation of vitamin D in the elderly in order to improve muscle strength and reduce falls; however the clinical studies have provided mixed results, without unequivocal proof of beneficial effects on strength and function, especially in frail elderly. Based on the fact that vitamin D is an inexpensive, safe and easy to implement intervention, this therapeutic option for the sarcopenia of the elderly merits further consideration.

7.5. Exercise in the elderly

The majority of studies in the elderly, both community-dwelling elders and nursing home residents and the frail, show that exercise has beneficial effects [133–136] and that resistance training increases strength in this age group.

Many of the published studies assessed lower extremity strength [136–138] and use a concentric exercise protocol. Most of the training intensity chosen in these studies was in the range of 70–80% of 1-RM (1-repetition maximum), which is the absolute maximum load that one can lift and is used in high-intensity resistance

training. The study duration varied between 2 and 25 weeks. The studies find an improvement of up to 163% in strength and about a 6% increase in thigh muscle volume with resistance training [139]. The relative increase in strength in the elderly was similar to that observed in young adults. Albeit the absolute gain was lower in the elderly [140–142]. This increase in strength results in improvement in mobility and increase in spontaneous activity in the elderly [135], which in part is explained by increased neural recruitment of existing underused skeletal muscle. The frequency of exercise necessary to delay functional decline, especially in frail older adults is unknown; however studies have shown a benefit from resistance training as few as 2 days per week [143].

Studies by Mackey et al. [144] demonstrated that 12 weeks of resistance training in the elderly results in an increase in the number of satellite cells in human skeletal muscle in older men and women. The expression of the IGF-I splice variant MGF, which is thought to have an impact on satellite cells, increases significantly in the quadriceps muscles of elderly men after resistance training for five weeks [145].

To date, the combination of GH and strength training in healthy older adults, tested in small group and short-term studies, has not shown additional beneficial effects on strength when compared to strength training alone [146,147]. These results could also suggest that GH in healthy older adults may not improve function or strength independently.

8. Difficulties in designing clinical trials to develop evidence-based interventions to prevent or delay functional decline among older persons

The main difficulties in designing a clinical trial in aging research relate to the selection of the outcome parameter, the duration of the trial, the selection of the appropriate study population and the lack in consensus definitions for key abnormal physiologic states (such as frailty, sarcopenia and others), which are prevalent in otherwise healthy elderly.

8.1. Selection of outcome parameter

In theory, an intervention tested in a clinical trial needs to show specificity of the effect and have a defined mechanism. It needs to result in a positive functional outcome and demonstrate an acceptable safety profile. The traditional concept of clinical trials has been to develop a compound or intervention that is targeted towards a specific disease with a disease-specific outcome in order to be able to evaluate the efficacy of the intervention. This concept is not applicable to randomized clinical trials (RCTs) in aging research because: multiple factors are involved in the development of frailty which ultimately results in the functional decline and loss of independence. Instead of focusing on one single disease, measures of functional status that describe the overall health status have been used and will be used more frequently in the future. The concept that these functional outcomes are not disease specific has made it difficult to get approval from the FDA [18].

When designing trials in aging research, the focus often is on preventing the development of disability [18]. It seems that there is still a lack of knowledge as to which are the best outcome parameters that predict the development of disability.

For example, it is unclear how improvement in strength or function has an impact on the well-being and daily life of the elderly and which functional outcome measures should be used for proof of efficacy of such an intervention. The frailty working group [148] describes the short physical performance battery (SPPB) and the gait speed measurement as two functional tests that are close to being ready for pharmacological trials in the elderly. Both tools assess lower extremity function and mobility.

Self-reported measures are often not collected under standardized conditions and reflect how the volunteer feels at the time of the testing rather than the usual daily performance at home.

The development of activity monitors that can be worn will allow future studies to monitor study subjects continuously in real time in their home environment. This has to be the gold standard measure as to whether or not the interventions really affect function and independence.

8.2. Duration of the study

Most of the outcome parameters of interest in an aging-related study show an active age-dependent decline. The prevention of such a decline in the treatment/intervention group can be considered as the desired study outcome. Only long-term placebo-controlled studies will be able to show such a slowing or prevention of the age-dependent decline in outcome parameters thought to contribute to the physical frailty of the elderly.

8.3. Selection of study population

The considerable heterogeneity in the older population group suggests that age alone is probably not the best selection criterion when designing a gerontological study. The optimal age range of the study population may vary depending on the specific intervention to be tested. In addition, the older the study group the more likely there will be a high dropout rate [18]. Standard criteria for inclusion of selected older populations often are missing. As pointed out by Ferrucci et al. [18] a rapid

decline in function in a subgroup of volunteers, might lead to a drop out from the study which could bias the results. On the other hand, the inclusion of fit, healthy older adults with no functional abnormalities can make it difficult to find significant changes because of ceiling effects.

9. Conclusion

Decrease in muscle mass has been shown to be a key element in the development of frailty. Hormonal interventions such as GH, steroids, ghrelin mimetics and possibly vitamin D have beneficial effects on lean body mass. GH treatment in the elderly is able to increase IGF-I levels, decrease fat mass and increase lean body mass, however without a demonstrable effect on strength or function. Ghrelin-mimetics which have the ability to increase caloric intake as well as to increase lean body mass in the older population, could be potentially beneficial and reverse the catabolic state and arrest and/or delay the development of sarcopenia and ultimately prevent/delay loss of independence. They have the advantage over GH in that they stimulate pulsatile GH secretion and restore levels to those seen in normal younger individuals and do not risk over stimulating the GH/IGF-I axis. In addition they are orally active and thus avoid the need for injections. While studies have shown beneficial effects of ghrelin mimetics on muscle mass, no effects have been found on function and strength in the elderly. Testosterone has been shown to have beneficial effects on body composition, with mixed results on function and possibly adverse effects on lipid levels. Sufficient clinical data supporting the use of vitamin D for prevention or treatment of muscle loss are currently lacking. The expected decrease in mortality of any therapy when applied to a sarcopenic population, needs to be carefully balanced with the safety profile of these interventions, such as the potential risk of cancer development or aggravating a diabetic tendency. Given the current and future demographic age shift in the world population, intense future research in this area is imperative. This includes, well designed long-term studies, validated outcome measures of function and the careful selection of study populations. Until the results of such studies are available, the broad use of GH, ghrelin mimetics, testosterone or vitamin D in the older population, albeit potentially beneficial, can not be recommended.

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