Frailty of Older Age: The Role of the Endocrine - Immune Interaction

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Abstract: The so-called demographic transition has changed the age structure of the population worldwide, with profound effects on societal organization. The growing number and percentage of old and very old people has compelled the scientific community to focus on age related diseases and peculiar consequences of aging itself such as disability and frailty. Understanding the pathophysiology of frailty, a syndrome characterized by a reduced functional reserve and impaired adaptive capacity that results from cumulative declines of multiple subsystems, and causes increased vulnerability to adverse outcomes, is a major topic in aging research. Aging processes induce multiple changes in the hormones network (menopause, andropause, somatopause and adrenopause), in the immune system, and can modulate their efficiency and effectiveness in determining a response to stressors. These triggering events can unmask frailty in older people. Starting from these assumptions, we analyzed the relationship of the endocrine and immune networks in aging and in the different domains that are characteristically associated with the frailty syndrome, such as disability and sarcopenia, as well as in diseases related to aging such as Alzheimer’s dementia and Congestive Heart Failure.

Key Words: Frailty; Hormones; Cytokines; Disability; Aging.

THE AGING SOCIETY AND THE PROBLEMS OF DISABILITY, CO-MORBIDITY AND FRAILTY

Progressive aging of the population has become a worldwide phenomenon. The demographic transition, characterized by reduced birth rates and reduced mortality rate across the life-span has affected both “developed” and “developing” countries, causing a growth of the “young old”, and especially of the “old-old” subjects (i.e. those 65-74 and 75-84 years, respectively) in the population.

The global population aged 65 or more was estimated to be 420 million in 2000, with an increase of 9.5 million over the previous year. Future projections indicate that the population growth will be similar to that seen until now, with more than 60 countries with ≥2 million people aged 65 and over by 2010, in comparison to 31 countries in 2000 [1].

As individuals live longer, quality of life becomes a central issue in health care. The medical and research community has shifted from the classic paradigm of health, based on acute diseases that in most instances are amenable to cure, to chronic diseases and disability which are generally considered as major determinants of the quality of life in older people.

Disability is defined as difficulty or need of someone else’s help in performing desired activities, important to one’s own quality of life, and/or carrying out self-care tasks (such as eating, washing oneself and moving from bed to chair) or instrumental activities (such as cooking, making telephone calls, or taking pills) of everyday life.

Physical disability is highly prevalent in older people. Between 20 and 30% of community dwelling adults older than 70 years report problems in performing everyday tasks without the help of another person [2].

Loss of mobility is an important form of disability, which is often operationally defined as difficulty or inability to walk across the room, with an incidence estimated to be 11.6/1000 person years [3].

Data from developed countries (Canada, United States, Austria and Finland) are inconclusive regarding the relationship between rising life expectancy and trends in disability expectancy over a 10-years interval at the beginning of the nineties [4].

In the Unites States, a decline in the incidence of disability was found, whereas an increase was observed in Austria, and lastly, in Canada and Finland no differences could be found in the disability free life expectancies in the same years [4]. More recent data (US National Long-term Care Survey) strongly suggests that the rates of disability are declining and this trend is primarily attributable to a reduction in the more severe forms of disability [4].
Unfortunately, rising cumulative incidence and prevalence of the major age-associated chronic conditions has paralleled the progressive increment in life expectancy. There is ample evidence that the condition of "co-morbidity" occurs more often that predicted by association due to pure "chance", suggesting that some individuals develop an excess global vulnerability to multiple diseases.

Many medical conditions, such as AD, CHF, type-2 diabetes and osteoporosis, could be considered as being age-dependent. These diseases are almost always attributable to degenerative processes where inflammation plays an important role; their age-related increased incidence and prevalence tend to mirror the logarithmic trend of raising mortality described by Gompertz' law [5-7]. Since these diseases cannot be cured, the emphasis is mainly on primary (delay the onset) and tertiary prevention (reducing or postponing a disability-related process). Somewhat related but also distinguished from co-morbidity and disability is frailty, a complex clinical entity characterized by the imbalance of the homeostatic capacity, which becomes particularly evident as inability to regain a stable homeostasis after a stressful destabilizing event.

Many researchers believe that the development of frailty is an intrinsic feature of the aging process and what distinguishes the individual is whether this process is accelerated or slowed compared to the average aging population. In other words, older people would be more likely to be frail with increasing age, but for some individual the process is so slow that is never clinically manifest. This is equivalent to say that "frailty is not an inevitable consequence of the aging process" [8].

The consequence of this interpretation is that both non-elderly frail subjects (mostly affected by chronic disorders or invalidating consequences of acute episodes) and elderly non-frail subjects (successfully aged) are to be considered, along with the definition of the most common examples of frail elderly subjects, conceptually different from those affected by age-associated diseases and disabilities.

The field of aging research is currently struggling to find an operational definition to be used in observational studies and in clinical trials [9]. Current definition based on combinations of clinical features is helpful but needs substantial refinement and validation.

HORMONES AND THE AGING PROCESS

The aging process induces multiple changes in the production, activity and clearance of hormones.

The release of hormones has a more disordered pattern in aged subjects, coupled with a decrease in hormonal receptor-function that leads to chaotic responses. The most important and apparent proof of changes in hormonal production over the aging process are menopause, andropause, adrenopause and somatopause [10].

It has been postulated that the clinical emergence of frailty after an acute, stressful event, such as a stroke or an hospital admission is related to a dysfunction of the physiological network that maintains the individual biological homeostasis, including the hormonal network [11].

Estimates of the crude prevalence of androgen deficiency (defined using both signs/symptoms plus total and calculated free T) range between 6.0 to 12.3%; the crude incidence rate of androgen deficiency is 12.3 per 1,000 person-years, and the rate increases significantly with age [12].

Total and free T levels decline in men during aging. The average decline of serum T is about 35% and the free fraction is reduced by half [13].

While T and Estradiol decrease with age, SHBG increases [14, 15], suggesting that an alteration of the balance between androgens and estrogens occurs in aging.

Many studies have supported the role of this imbalance to explain the loss of muscle mass and strength during aging [16-21]. Cognitive function also seems to be affected by this androgen/estrogen disequilibrium [22, 23].

Human ageing is associated with a declining activity of the GH/IGF-1 axis. These changes in the axis activity are mainly dependent on age-related variations in the hypothalamic control of somatotropic function, which is also affected by changes in peripheral hormones and metabolic input (i.e. physical activity) [24].

Sex Differences

Over the aging process, the trajectory of health and functional status is quite different in men and women. Women tend to live longer than men but surprisingly spend a larger portion of their life with disability and multiple chronic diseases. Accordingly, in the last decades of life, women are more susceptible than men to AD and coronary heart disease.

Both disability and susceptibility to co-morbidity have been attributed to dysregulation in the production, handling, delivery and utilization of metabolic energy across different cells and tissues.

This complex network includes most hormones, pro and anti oxidative factors and immuno-modulatory substances, such as pro- and anti-inflammatory mediators [25-31].

There is a large body of evidence from animal and human studies that gender-related changes in the levels of circulating hormones lead to, or are related to, imbalances in the immune system [32].

In female mice, stimulation with IL-1β induces the release of cortisol in response to lower doses of cytokine compared to males [33].

In healthy blood donors serum levels of DHEA-S were negatively associated with serum IL-6 and sIL-6R, but only in male subjects. In the same study, serum sIL-6R and TGF-β1 levels were not correlated with age in either sex, and were not significantly different between sexes [34].

These observations are typical examples of the effect of cytokines, particularly IL-6, in modulating the endocrine system in a gender specific fashion.

NEURO IMMUNE ENDOCRINE INTERACTION

A reduction in physiological reserve occurs naturally during the aging process. It may be linked to a loss of performance in the metabolic network that regulates the energy distribution. Several lines of research suggest a bi-directional
synergy between the central nervous system and the endocrine system in this context [35-37]. For example, it has been suggested that pro-inflammatory cytokines down-regulate the response to many hormones including insulin, GH, IGF-1, T and estrogens [38].

In both the hypothalamus and the hypophysis, but notably not in the adrenal glands, receptors for IL-1, IL-6 and TNF-α have been described, providing anatomical substrates for actions of these cytokines.

The interface between neuro-endocrine and immunological systems seems to be therefore provided by cytokines; one of the clearest demonstrations of this interaction is the response to danger signals during infection resulting in fever and its subsidiary effects on “sick” behavior, including sleepiness, reduced appetite [39], depressed mood that are often developed during prolonged stress [40].

A “cholinergic anti inflammatory pathway” which has been recently described [41], provide a new link between the two systems (parasympathetic nervous and immune). Preclinical data suggested that the stimulation of the vagus nerve down-regulates the production of TNF-α from macrophages, whereas its surgical severing sensitized animals to endotoxin shock. These data suggest that the parasympathetic system may have a pivotal role in modulating the inflammatory response through a fast and efficient mechanism that suppresses the macrophage activation when it is excessive or no longer required.

Proinflammatory cytokines (IL-1, IL-6 and TNF-α) can directly modulate the release of GH, GH-RH and somatostatin through specific pituitary receptors [42]. Alternatively the same cytokines can decrease the serum concentration of IGF-I, acting through the inhibition of the GH–IGF-1–I–IGF-1-binding protein axis [43].

In a study comparing non-frail versus frail older people [44], lower serum levels of IGF-1 and DHEA-S were found in the latter group, defined by a set of five clinical criteria, as reported by Fried et al. [45]. Moreover, an inverse correlation between serum IGF-1 and IL-6 was observed only in the frail elderly. It is suggestive that both altered endocrine profile and inflammatory mediators may contribute to the pathogenesis of the frailty syndrome.

Immune stimulated adrenal secretion is thought to occur through a direct action of several pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) in the median eminence of the hypothalamus inducing CRH production, which in turn stimulates the secretion of ACTH from the pituitary [46]. However controversy still remains regarding the main site of action of cytokines on glucocorticoid secretion, since the effect on this neuro-endocrine axis has also been observed following ablation of the hypothalamus.

An increased production of pro-inflammatory cytokines can therefore compensate for the impaired HHA axis function and activate inflammatory ACTH and cortisol responses in mice deficient in CRH [47].

IMMUNOLOGICAL CORRELATES OF FRAILTY

Several lines of evidence suggest that a mechanism of immunosenescence contributes to the decline of physiological functions that occur over the aging process. With aging, the immune system becomes less able to respond to signals coming from the internal and external milieu [7]. Antigenic experiences that accumulate over the life span are phenotypically represented by clonal expansions of memory T and B lymphocytes, with a proportional reduction in the “immunological space” left to ensure bodily defences against infection and cancer [48]. This remodelling of the immune system is also accompanied by the appearance of non-pathogenic organ non-specific autoantibodies and chronic low grade increase of inflammatory markers [49, 50]. In frail elderly subjects such changes seem to be even more evident, due to the stress induced by both chronic antigenic load and oxidative damage, leading to heightened pro-inflammatory setting which predisposes to multiple age-associated degenerative diseases [6, 51] (see also Salvioli S. et al., this issue). However, the most well-preserved components of the immune system are those that respond to general stressors, and are influenced by age-related alterations in the HHA axis. In this respect, innate immune response mechanisms, which discriminate the danger signature associated with environmental substances able to cause damage and disease, seem to be the first line of defence and the last to reduce its efficiency. A decreased capacity to respond to danger signals has been reported to represent a predictive marker for frailty in the Leiden 85-plus study [52]. Irrespective of their pro- or anti-inflammatory profile and independent of disease, a pattern of low production of cytokines upon ex vivo stimulation with lipopolysaccharide was associated with an elevated mortality. The coexistence of seemingly divergent findings when looking at the cytokine pattern [53, 54] or their global production, and from the point of view of clonally and non clonally distributed receptors-bearing immune cells (in other words, cells belonging to the adaptive or the innate immune systems) further complicate our understanding of the contribution of immunosenescence to frailty [51, 55, 56].

FRAILTY DEFINITION AND PATHOPHYSIOLOGY

The “frail elderly” syndrome is a complex clinical entity and until now, agreement between a standardized definition and an empirical basis is lacking.

Many possible definitions of frailty have been proposed in the literature, a large number of different and often conflicting criteria were used ranging from non-disabled older people to old-old, bedridden subjects with multiple end stage medical conditions [57].

Frailty was often erroneously used interchangeably with disability, co-morbidity or advanced old age. Recently, Fried and collaborators attempted to clarify differences and analogies between these four concepts and discussed their inter-relationship [45] (Fig. (I)).

Clinically the frailty syndrome is characterized by wasting (muscle, strength and unintentional weight loss), reduction in endurance, balance and mobility. Although decreases in cognitive performance is not part of the most acknowledged definition of the frailty syndrome, many researchers claim that poor cognitive function should be considered a core component of the frailty phenotype.

The identification of the measurement domains that should be used to characterize the clinical phenotype of
Frailty was developed and validated in a survey conducted among a large number of geriatricians. Ninety-seven percent of those interviewed supported the hypothesis that frailty involves multiple physiological systems and functions and cannot be defined according to one simple criterion. Accordingly, there was agreement on the concept that a specific disease, isolated or in combination, could not be considered as adequate marker to identify the typical frail elderly [45].

The concept that frailty is a biological syndrome with a decreased functional response reserve to events, resulting from cumulative declines of multiple subsystems and vulnerability to adverse outcomes also emerged from the analysis of conceptual models developed over the last decade [2, 55].

A biological model, the “cycle of frailty”, that includes sarcopenia (the loss of muscle mass and strength), neuroendocrine decline, and immune dysfunction as potential causes, was proposed. The cycle or downward spiral can be precipitated by “trigger events” [8].

These stressors events could be of a different nature, such as an acute disease (i.e. stroke, bone fracture), prolonged hospitalization, environmental changes (for example from stress related to moving home) and social bereavement (the loss of one’s role in the society).

In general, subjects at risk of becoming frail are in a state of precarious but stable homeostasis, which is maintained by the use of compensatory strategies, and can be unmasked by stressor events [2], or using challenging tests of objective performance, such as the Short Performance Scale [9, 58].

Men seem to be less prone to develop frailty than women [59]. Neuroendocrine and hormonal factors, including T, GH and cortisol in addition to immune system dimorphism may explain the male advantage in muscle mass maintenance over the entire life span compared to women.

The net effect of the hormonal deregulation and immune system dysfunction is an accelerated loss of muscle mass [11, 45, 57, 60, 61]. The consequences of sarcopenia are loss of mobility, neuromuscular impairment, and homeostatic balance failure syndrome with gait and balance disorders [55]. All these elements contribute to disabilities and are important factors in increased fear of falling and falls.

Another component of the frail loop syndrome is the decline of the nutritional reserve [45].

In conclusion the clinical definition of frailty is rarely encompassed by a single altered system, but instead by multiple physiological systems.

PREVALENCE

Lacking an agreement about the clinical and operational definition of frailty, estimates on the magnitude of this phenomenon vary widely in the literature.

Based on the presence of a critical mass of three or more core frail elements with the core entities being weakness, poor endurance, weight loss, low physical activity and slow walking speed, in the Cardiovascular Health Study on a sample of 4317 community-dwelling adults aged 65 years or older, who lived in four communities in the United States, 7% of this population could be defined as frail, the proportion increased steadily with age, up to 30% of those 80 years or older [2] (Fig. (2)).

Using the Geriatric Status Scale, which combines aspects of cognitive and functional performance to describe various degrees of frailty, the Canadian Study of Health and Aging found a prevalence rate among those subjects aged 65 to 74 of 70 per 1000 persons/years, 175 per 1000 among those aged 75 to 84 and 336 per 1000 of those aged 85 years and older [62, 63].

The prevalence of frailty was assessed in the Amsterdam Longitudinal Aging Study, using a definition based on three or more frailty markers. Frailty as a static prevalent condition was studied in the second follow-up, while the dynamic definition was based on the change of the score between two assessments. The authors found that women were at higher risk of being affected by static frailty (18.6% vs 13.6% in males) while the risk of developing a dynamic frailty was similar in men and women (18.3% vs 17.0%) [64].
COMPONENTS OF FRAILTY

Disability

Throughout adult life, all physiological functions gradually decline [65]. Most aging individuals die from cardiovascular diseases, cancer or dementia; nevertheless, in a growing number of older adults loss of physical function is the limiting factor that determines their likelihood of maintaining a fully independent life until death [66].

Although several chronic conditions, that are highly prevalent among the elderly have been recognized as powerful risk factors for frailty and physical disability [67, 68], many older adults become disabled in the absence of chronic disabling conditions [45]. Age-related frailty is characterized by generalized weakness, loss of muscle mass and strength, impaired mobility and balance, and poor endurance [69]. Changes in body composition and loss of muscle mass and strength are important phenomena in the process of frailty [70]. In older people loss of muscle mass and strength, a process referred to as sarcopenia, has a multi-factorial pathogenesis, including chronic diseases, malnutrition, sedentary lifestyle and decreased physical activity [71, 72]; physical decline during aging has been considered as physiologic, at least partially, nevertheless a growing bulk of evidence is now supporting an important role of the endocrine and the immune systems [10].

From a clinical perspective the two most important changes in the endocrine activity during aging involve the pancreas and the thyroid. More than one third of individuals older than 65 have impaired glucose tolerance or diabetes mellitus [73]. These people are at high risk of developing macrovascular complications, including coronary artery disease and stroke. However, recent studies clearly demonstrated that, independent of traditional micro- and macrovascular complications, older people with diabetes develop a number of age-related health outcomes, including mobility and self care disability, falls, depression, cognitive impairment, and dementia, that are considered common geriatric syndromes [74-76]. Age related thyroid dysfunction is also common in older people. However, at present, a change in plasma thyroid hormones and thyroid-stimulating hormones has not been convincingly related to physical and functional performance.

Three other hormonal systems are characterized by a decrease in circulating hormones over the life-span: the sex hormone system (estradiol, T), the DHEA and it sulphate system, and the GH/IGF-1 axis [10].

Age-associated changes in T levels occur slowly and insidiously [77]. T has long been known for its anabolic effects; no studies, however, have formally investigated to date the relationship between circulating T levels and physical disability in older eugonadic individuals. Conversely, a number of small clinical intervention trials have demonstrated that older men are as responsive as young individuals to the anabolic effect of T on the muscle [78]. T replacement therapy in older men increases fat-free mass, muscle strength, leg power, and decreases fat-mass [79]. The anabolic effect of T is mediated by multiple mechanisms, including a modulating effect on pluripotent mesenchymal cells [78]. However, whether T therapy improves physical function or reduces the risk of disability remains to be established [80].

Animal studies suggest that DHEA-S administration prevents obesity, diabetes, cancer and heart disease, while enhancing immune function. Data from human studies are scant and controversial. It has been reported that older men aged 90 and older with the lowest DHEA-S level have poorer functional performance in activities of daily living [81] and small clinical studies also suggested a positive relationship between DHEA-S and muscle power. Nevertheless the results of randomized clinical trials did not fully confirm these observations. Recently, data from the InCHIANTI, a large population-based epidemiological study, suggested that
serum DHEA-S is independently correlated with muscle strength and mass, but only in men between 60 and 79 years of age, suggesting that the effect of DHEA-S on skeletal muscle might be maximal during certain critical periods [82].

Conflicting results have also been collected for the hypothesis that somatopause contributes to the aging-related functional decline. Indeed, while GH replacement therapy in GH-deficient adults was shown to increase muscle mass, strength, and quality of life, GH administration to healthy elderly individuals failed to increase muscle strength and maximal oxygen consumption [83]. With regard to physical disability, only a few studies have investigated the relationship between the GH/IGF-1 system and this more distal outcome. All have failed to demonstrate a significant association [84, 85]. More recently, a population-based study of community-dwelling women aged 70-79 reported a significant cross-sectional relationship of low IGF-1 serum level with poor knee extensor muscle strength, slow walking speed, and self-reported difficulty with mobility tasks [86]. These findings have been subsequently confirmed by a longitudinal analysis from the same population [29]. Of note, this work suggests, for the first time, an aggregate dysregulation effect in endocrine and immune systems. Indeed, women with low IGF-1 (lowest quartile) and high IL-6 levels (highest quartile) were at greater risk for death as well as incident walking limitation, mobility disability, and disability in activities of daily living compared with those with high IGF-1 and low IL-6 levels.

The involvement of the immune system in the pathogenesis of the age-related decline and physical disability has been hypothesized for many years [87]. The serum concentration of many inflammatory cytokines increases with age. Inflammation has been associated with increased morbidity and mortality in elderly people [28, 88]. In the last years several studies have directly evaluated the relationship of IL-6 and other important cytokines with physical function and physical disability. Globally taken these studies have consistently demonstrated that increased levels of IL-6 and other serum markers of inflammation are associated with a risk of physical disability in late life [89, 90]. A direct role of inflammation in the development of disability can be hypothesized based on the catabolic effects that pro-inflammatory cytokines may have on muscles and on the results of several studies suggesting a strong relationship of these nonspecific markers of inflammation and loss of muscle mass [30, 91, 92]. However, the synergistic effect of the hormonal and immune systems provides a new perspective into the complex biological pathways underlying the pathogenesis of frailty and physical disability.

**Sarcopenia**

A decrease in lean body mass and an increase in fat mass occurs with aging [93, 94] (Fig. (3)).

The loss of muscle strength, mass and quality with advanced age (structural composition, innervation, contractility, capillary density, fatigability and glucose metabolism), results in a condition known as sarcopenia [71, 95, 96].

Lean mass begins to decrease after age 60 and accelerates after age 80, while skeletal muscle mass is estimated to undergo a reduction of 20-30% during the entire life span in normal healthy subjects [95], reaching a 50% decrease in total muscle mass by age 90 [97]. While there is general agreement that older people tend to become sarcopenic, there is substantial disagreement about the criteria that should be used for the definition of sarcopenia.

In fact, the word sarcopenia is used interchangeably to describe age-related muscle loss as the clinical condition of

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**Fig. (3).** Muscle mass difference in a young (left) and an old woman (right). Images were derived from the InCHIANTI database, and were obtained using Peripheric Semiquantitative CT scan at 2/3 of the distance between the external malleolus and the intrarticular space of the knee. The reduction in muscle mass, bone thickness and increase of fat mass can be appreciated.
exceptionally low levels of muscle mass [98]. The most important consequence of lower muscle mass is its association with lowered strength and functional limitation and disability [97, 99, 100].

Regardless of the precise definition, the prevalence of clinically significant sarcopenia is estimated to range from 8.8% in young-old women to 17.5% in old-old men [60].

Many candidate mechanisms may lead to sarcopenia, including age-related declines in peripheral nerve function, hormone network, sex steroid levels, and physical activity [61]. Additionally, fat gain, increased production of catabolic cytokines, and inadequate intake of dietary energy and protein are also potentially important causes of sarcopenia [101, 102]. The relative contribution of each of these factors is not yet clear.

Hormones are key regulators of human muscle metabolism: in fact muscle is one of the most metabolically active tissue in the body. Its metabolic flexibility combined with its capacity to store substrates, make it an ideal hormonal target [103].

Skeletal muscle protein undergoes continuous remodeling, depicting the homeostatic balance between anabolic and catabolic processes: these processes are present during growth, health, disease and aging.

Cross-sectional epidemiological studies have supported a role for T in the loss of muscle mass and strength. Both longitudinal and cross-sectional studies have shown that T declines with aging in men and, because of the increase in SHBG, there is an even greater decline in free or bioavailable T [104].

In women T declines approximately by one half between the ages of 20 to 40 [11].

T supplementation in men increases muscle mass, power, bone mineral density and decreases body fat [105, 106]. Moreover T seems to partially inhibit detrimental glucocorticoid-induced increases of pro-inflammatory cytokines after stressor events [107].

After menopause/andropause, serum IL-6 levels rise, even in the absence of infection, trauma, or stress. IL-6 plays a stimulatory role for acrophase pituitary and peripheral hormone secretion, apparently more so in women.

The gender-specific changes of cortisol in relation to ACTH depend on the age-related decrease of the respective sex hormone and the increase of IL-6 in females [32, 108].

The net effect of estrogens on muscle mass and muscle strength has been poorly investigated. Estrogen receptors have been found in muscle cells and therefore estrogens are also likely involved in the metabolic control of this tissue.

Studies assessing the role of HRT on muscle mass and strength provided uncertain results both on real benefits of HRT on muscle and its effects on muscle metabolism [109-111].

Aromatase expression in adipose tissue accounts for the extraglandular (peripheral) formation of estrogen and increases as a function of body weight and advancing age. Sufficient circulating levels of the biologically active estrogen, estradiol, can be produced as a result of extraglandular aromatization of androstenedione to estrone [112].

The regulation of aromatase expression in human cells can be activated or inhibited by various hormones. A number of factors, including IL-6, TNF-α, and PGE2, which can stimulate aromatase activity, have been identified.

Macrophages and lymphocytes that infiltrate breast tissue are now thought to be an important source of cytokines that can stimulate aromatase activity in this tissue. As plasma concentrations of some cytokines increase during menopause, increased peripheral aromatase activity is detected in older women [113] and consequently changes in body composition, such as loss of fat-free mass, a potential a decline in skeletal muscle mass, a loss of muscular strength and a decline in physical activity are observed [114].

The age-related changes of the GH/IGF-1 axis activity are mainly dependent on age-related variations in the hypothalamic control of somatotrophin function. The term "somatopause" indicates the potential link between age-related decline in GH and IGF-1 levels and changes in body composition, structural functions and metabolism which characterize aging [24].

The administration of rhGH, when given to deficient adults, induced persistent increases in isometric knee flexor strength, concentric knee flexor strength, and peak grip strength [115]. However, these positive effects were associated with frequent and substantial side effects. At present, however, there is no definite evidence that "frail" elderly subjects really benefit from restoring GH and IGF-1 levels within the young adult range [24].

GH administration in the elderly induces an increase of IGF-1 levels, which causes skeletal muscle hypertrophy [116].

Chronic inflammation, namely IL-6, may reduce physical function through inhibiting local IGF-1 muscle expression [21]. On the contrary, myostatin seems to be related to muscle mass loss particularly in subjects carrying a change at codon 55 in exon 1 (A55t) and a substitution in exon 2 (K153R) [117, 118].

Considering the paramount evidence of the interaction between the hormones and the immunological networks in the pathogenesis of sarcopenia, some doubts arise from a recent study on functional and morphological changes occurring with age in the non parasitic nematode C. elegans [119]. It has been found that aging worms develop sarcopenia starting in the post reproductive period, but sarcopenia does not develop in a stereotyped fashion. It develops at different ages within a cohort of genetically identical worms. The sarcopenic process has important functional consequences, as a progressive decline in mobility, and could be considered the best single predictor of mortality, even better than age itself.

The finding of sarcopenia in the worm suggests that the causes of sarcopenia may lie within the aging muscle itself. In fact the hormonal milieu of the worm is substantially different from that present in mammals, being devoid of sex hormones and some cytokines as IL-6. Moreover, in contrast to mammals, low levels of IGF-1 have been associated with an increase in longevity and in prevention of sarcopenia.
Interestingly, the worm’s nervous system remains largely unaffected by the aging process.

Globally all these considerations and the presence of a high number of mitochondria suggest the prediction that muscles mass in C. elegans may be more susceptible to oxidative damage and mitochondrial dysfunction [120].

Probably also in this case, as in the case of the theory of aging, the two opposite viewpoints: hormones and immune network interaction on one side, and oxidative damage on the other, could have specific but overlapping roles in the genesis of sarcopenia.

Bone Loss

In recent years, much attention has been focused on identifying the cytokines involved in the control of osteoporosis. To date, several candidate cytokines have received attention, among them TNF-α, IL-1β and the IL-6/M6R system. Several lines of evidence indicate that the decline in ovarian function with menopause is associated with spontaneous increases in pro-inflammatory cytokines [121-124]. In vitro and in vivo animal studies have shown that a close link between sex steroids and a pro-inflammatory state contributes to the post-menopausal bone loss.

The effect of estrogen on bone metabolism is well known and there is overwhelming evidence that the decline in estrogens level during menopause contributes to post-menopausal osteoporosis, and indirectly, to the higher incidence of osteoporotic fractures in men than in women. Interestingly, pre-clinical studies suggested that sex hormones prevent bone loss by blocking the production of pro-inflammatory cytokines by bone marrow and bone cells [125], and perhaps by blocking their biological activity on OC. The main consequence of increased cytokine production in the bone micro-environment is an expansion of the osteoclastic pool due to increased OC formation and elongation of their life span [126]. Examples of this phenomenon are the differentiation of stromal cells precursors in "high osteoclastogenic" stromal cells, as a result of the increased bone marrow levels of TNF-α induced by estrogen deficiency [127], and the differentiation of cells of the monocytic lineage into OC in response to factors produced by stromal cells, such as IL-6.

According to recent views, chronically elevated levels of IL-6, IL-1Ra, and CRP likely reflect local ongoing TNF-α production that cannot be detected in the circulation because is rapidly degraded. In accordance with this theory, TNF-α is the primary inducer of a chain of events that configure the acute-phase response, and involves the production of a number of pro-inflammatory cytokines [128] which, in turn trigger OC production. The demonstration of this hypothesis would be a crucial finding for a new pharmacological approach for osteoporosis. In fact, recent studies have provided key evidence that antagonizing TNF-α is a viable therapeutic strategy for clinical use [129].

There is little evidence that circulating levels of pro-inflammatory markers are strong, independent predictors of osteoporosis and/or osteoporotic fractures. This is not completely surprising since the effect of cytokines is probably local and is only partially and indirectly reflected by circulating levels.

However, a number of studies have shown that single nucleotide polymorphisms of genes coding for specific cytokines are associated with different bone mineral density, both in clinical series and in large samples representative of the general population [130-134].

New approaches for osteoporosis therapy are urgently needed in frail older people, where a high grade of comorbidity is associated with high levels of cytokines [135].

Selectively blocking cytokines that increase bone turnover and accelerate cortical bone loss, might allow the reduction of the negative clinical outcomes in frail older people such as vertebral and femoral fractures.

However, until now treatments approaches based on the selective blockage of specific cytokines have produced conflicting results.

Dementia, Inflammation and Hormones

Cognitive function displays a progressive impairment with aging, and this is thought to be due to the accumulation of neuronal loss, senile plaques and neurofibrillary tangles, the major constituents of which are the Aβ (arising from a proteolytic cleavage of the amyloid precursor protein) and tau protein (abnormally phosphorylated microtubule structural molecule) respectively, which represent the hallmark of AD, a disease characteristic of older individuals where the chronic damage to the brain cortex leads to decreased ability of older persons to cope with daily events and ultimately to loss of self-sufficiency.

A wealth of studies has demonstrated that inflammation occurs in the brain of patients with AD. Although it is not clear when and why the inflammation begins, the current view is that neuroinflammation is not simply an epiphenomenon but rather a pathophysiological event in AD [136].

The sources of inflammation in the Alzheimer brain have been intensively investigated. Glia, including both microglia and astrocytes, plays a primary role in this neuroinflammatory process, although neurons might also be involved [137]. Microglia are attracted and activated by Aβ deposits, which in turn can be produced by these cells.

In particular IL-1, synthesized and released by activated microglia, is implicated in the formation of neuritic plaques, and in excessive tau phosphorylation and tangle development, two central processes in neurodegeneration.

Several cytokines, such as IL-6, TNF-α, TGF, along with chemokines, pentraxins (C reactive protein and amyloid P), the complement system, cyclooxygenase-derived prosta-glandins and the coagulation and fibrinolysis systems participate in the complex network of inflammatory processes that have been found to take place in AD brain [136, 138].

Glia activation occurs with normal aging, although to a lesser degree than that observed in AD, as well as in conditions that increase the risk of AD, such as head trauma and Down’s syndrome.

Despite the epidemiological evidence supporting their benefits, anti-inflammatory drug use towards the risk or the progression of dementia is controversial [139, 140]; the few clinical trials performed with these drugs have produced...
negative results [141-144], but this might be partially due to methodological weaknesses in study design [145]. On the other hand these disappointing results, together with increasing evidence that some inflammatory pathways can be neuroprotective, testify that the role of neuroinflammation is not fully understood.

Even more obscure and controversial is the relationship between hormones and dementia. The best example is probably the unexpected finding that HRT did not improve cognitive functions [146, 147] and even increased the risk of dementia in post-menopausal women [148]. This result is conflicting with a large amount of in vitro, animal and epidemiological data supporting the neuroprotective effects of these hormones [149, 150]. In particular estrogens have neurotrophic effects on the brain and influence several neural transmitters, particularly acetylcholine, that have a crucial role in cognitive functions, since these hormones cause an increase in the synthesis of coline acetyltransferase and hence of acetylcholine. Moreover estrogens can protect neurons against excitatory aminoacids and beta amyloid toxicity, enhancing neuronal survival and recovery [151].

Corticosteroids have also been strongly related to neurodegeneration since high levels of cortisol have been associated with atrophy of the hippocampus, a crucial structure for the maintenance of memory functions [152]. On the other hand, their powerful antiinflammatory activity might be useful to reduce neuroinflammation, although the only clinical testing the effectiveness of corticosteroids treatment in patients with Alzheimer’s disease did not show any efficacy [153].

Other potential therapeutic targets for dementia treatment are insulin and IGF-1, which have been shown to exert a neuroprotective effect, by influencing β amyloid peptide metabolism and clearance as well as by increasing Tau phosphorylation, to promote neurogenesis and to antagonize TNF-α mediated inflammation [154].

Standard treatment with IACHE has been found to partially affect the inflammatory state by increasing potentially antagonistic cytokines such as IL-4 [25].

In summary, although inflammation and hormones are clearly involved in the pathogenesis of dementia, more research is needed to achieve a clear and full comprehension of their precise actions and to guide the use of antiinflammatory as well as hormonal agents for preventive and therapeutic purposes.

Diseases: the Example of Cardiovascular System Failure

Overproduction of IL-6, a pro-inflammatory cytokine, is associated with a spectrum of age-related conditions including cardiovascular diseases, one of the leading causes of frailty and death in older people. The link with cardiovascular disease is only partially understood. Inflammation and pro-inflammatory cytokines are important mediators in the development, progression and clinical evolution of atherosclerotic lesions, especially in coronary arteries and in the lower limbs vessels.

Interestingly, IL-6 is the most powerful stimulus for the up-regulation of CRP, which is now recognized as an important marker of cardiovascular risk and is widely used in clinical practice.

As gauged by this robust biomarker, inflammation predicts the prognosis of old patients with acute coronary syndromes [155].

Type-2 diabetes is a well recognized cardiovascular risk factor: serum levels of acute-phase reactants (including cortisol) and IL-6 show a gradual increase with increasing features of the metabolic syndrome in Type-2 diabetic patients [156].

Recent studies have shown that pro-inflammatory cytokines (IL-1β, IL-6, IL-10 and TNF-α) are involved in cardiac depression and in the complex syndrome of heart failure [26, 157]. Cardiac cachexia has been ascribed to neurohormonal alterations, like anabolic/catabolic imbalance and increased cytokine release [158].

IL-6 is a potent stimulator of CRH, a mechanism that leads to increased plasma cortisol levels; elevation of ACTH and cortisol can provoke multiple adverse cardiovascular reactions [159]. ANP is positively related to ejection fraction, adrenaline and noradrenaline concentration; while BNP is positively related to age, NYHA class, IL-6, TNF-α, adrenaline, noradrenaline and cortisol, while negatively with ejection fraction and FT3 in subjects suffering of CHF. These data confirmed a progressive activation of hormonal and immunological systems in patients with these diseases [160].

Depression, physical and psychological stressors, can affect the cardiovascular system because they enhance the production of pro-inflammatory cytokines, including IL-6 [161]. Vital exhaustion (a state characterized by fatigue, irritability, and general malaise that precedes the onset of coronary artery disease) is frequent in the elderly: stress-related changes in haemostasis and infection/inflammation may constitute important pathways that link vital exhaustion to cardiovascular disease, since it reflects an adaptive response of the host that is triggered by pro-inflammatory cytokines [162].

The link among the cardiovascular system, cytokines and the HHA axis is well documented by the sepsis model: there is a growing body of evidence that the use of low doses of steroids in patients with septic shock and relative adrenocortical insufficiency can improve outcomes relative to time to vasopressor withdrawal and 28-day mortality via anti-inflammatory, cardiovascular, and endogenous catecholamine enhancing effect [163].

CONCLUSIONS

The delicate balance needed to coordinate the action of several systems whose main functions are the regulation of responses to inner and outer stimuli and the permanent maintenance of bodily structures ensuring such activity is finely tuned during the individual’s life span. However, small changes accumulating in one system may reverberate on others, as in the case of the hormonal and immune networks, leading to disequilibrium and chaotic responses. We have chosen to address the particular issue of frailty in elderly subjects since it is paradigmatic of the interplay of dif-
different factors (hormones, immunity and stress) causing a decrease in several other systems (brain, heart, muscle, bone) and constantly crossing with disability and disease. The accumulated evidence points to common factors predisposing to all these age-associated features, which are by no means inevitable consequences of the aging process per se. So far only a few actors have been unveiled and many others may still be hiding, which may come to light through the accurate analysis of biological variables in epidemiological studies.

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ABBREVIATIONS

Aβ = beta amyloid protein  
ACTH = Adrenocorticotropic Hormone  
AD = Alzheimer’s Disease  
ANP = Atrial Natriuretic Peptide  
BNP = Brain Natriuretic Peptide  
CHF = Congestive Heart Failure  
CRH = Corticosteroid-Releasing Hormone  
CRP = C-Reactive Protein  
DHEA-S = Dehydroepiandrosterone Sulphate  
FT3 = Free Triiodothyronine  
GH = Growth Hormone  
GHRH = Growth Hormone-Releasing Hormone  
GHRH = Growth Hormone-Releasing Hormone  
HHA = Hypothalamic – Hypophysis – Adrenal  
HRT = Hormone Replacement Therapy  
IACHE = Inhibitors of Acethyl-Cholinesterase  
IGF-1 = Insulin-Like Growth Factor 1  
IL = Interleukin  
IRB = Inspiratory resistive breathing  
NYHA = New York Heart Association score  
OC = Osteoclast  
PGE(2) = Prostaglandin E 2  
rhGH = Recombinant Growth Hormone  
ROS = Reactive Oxygen Species  
SHBG = Sex-Hormone Binding Globulin  
T = Testosterone  
TGF = Transforming Growth Factor  
TNF = Tumor Necrosis Factor  

REFERENCES

References 164-166 are related articles recently published in Current Pharmaceutical Design.

[27] Paganelli R, Di Iorio A, Patricelli L, Ripani F, Sparvieri E, Faricelli R, et al. Proinflammatory cytokines in sera of elderly patients with dementia: levels in vascular injury are higher than those of mild-


