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The Different "Ageings" and their Importance to Achieve an Adequate Chronic Disease Assessment and Treatment

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Abstract

There are many "ageings": normal ageing, successful ageing, and pathological ageing or senescence, which should be clearly differentiated since they have different impact on elderly health. Senescence implies the presence of frailty status, and its combination with some chronic disease (eg: chronic kidney disease, etc.) can lead to a senescent variety of these conditions (eg: senescent nephropahy, etc.) which have worse evolution and prognosis compared to the original condition, and requires not only to treat the patient´s basal chronic disease but also his/her frailty phenotype. Therefore, is crucial to evaluate frailty phenotype in every patient, independently of his/her age, who suffers from a systemic chronic disease in order to distinguish chronic disease from its senescent form since they could have different prognosis, as well as diagnostic tests and therapeutic requirements.

Keywords: Ageing; Senescence; Frailty

Introduction

Normal ageing is a universal asynchronic and heterogeneous process which induces a series of changes in the organisms through time, characterized by the attenuation of functional performance compared to the maximal functional strength reached around the second decade of life. It is universal since it is part of everybody´s vital cycle, asynchronic because it has its particular rate in each individual, and heterogeneous because it has its particular rate in each individual´s organ [1]. However, there are at least two more sort of " ageings ": On one hand, the pathologic ageing or senescence which appears when ageing related changes are excessively (quantitatively and /or qualitatively) marked and significantly reduce the homeostatic capability of the organism making the individual vulnerable and frail [2]. On the other hand, the successful ageing which is unusual, and appears when ageing related changes are slightly (quantitatively and qualitatively) marked, leading to insignificant functional changes compared to young individuals. In this sense, it is worth pointing out that due to the asynchronic nature of the ageing process successfull ageing of one organ (eg: a kidney with a normal glomerular filtration rate value) can coexist with pathologic ageing of another organ (eg: a brain affected by dementia) [3].

Frailty is a phenotype of unsuccessful aging (senescence) characterized by a reduced homeostatic capability and a limited ability to respond to stressors. This phenotype is associated with an increased risk of disability, hospitalization and death. Several criteria to diagnose frailty have been proposed [2-5]. According to Fried Criteria, frailty is defined by the presence of significant impairment in at least 3 of 5 domains: weight loss, weakness, poor endurance and energy, slowness, and low physical activity level (Table 1) [6]. In addition, another validated and useful tool for frailtyrecognition is the clinical frailty scale (Table 2) [7,8]. Besides, even though physical performance can be assessed by several clinical tests, gait speed appears to be the most recommended one since it has been proposed as a life expectancy predictor. Gait speed has been validated with different distances and different time cut-offs and shows a strong association with frailty. Slowness measured by gait speed is a powerful predictor of poor outcome and mortality [2,5,9].

1 Weight loss: ≥10 pound (4.5 kg) of unintentionally weight loss in last 12 months.
2 Weakness: Grip strength in the lowest 20 % at baseline, adjusted to gender and body mass index.
3 Poor endurance and energy: Self-report exhaustion.
4 Slowness: Walking time/15 feet (4.5 m) - slowest 20 %. The slowest 20 %, adjusting to gender and standing height.
5 Low physical activity level: Kilocalories (Kcals) expended per week - lowest 20 %.
3 or more is frail Positive for 1 or 2 is prefrail or intermediate

Table 1: Fried frailty phenotype and its five domains.

Renal "ageings" and senescent nephropathy

The above exposed concepts have already been documented in the nephrology field, where the concepts of normal renal ageing, successful renal ageing, and senescent

nephropathy have already been reported and clearly distinguished [1-3]. In this case, normal age-related renal functional decline has been distinguished from chronic kidney disease (CKD) since in normal renal ageing glomerular filtration rate (GFR) reduces at a particular rate (1 ml/min since 40 years of age), showing normal serum urea, creatinine, hemoglobin, calcium, phosphorus, parathyroid hormone levels, as well as normal urinalyses and renal ultrasound image [1].

1 - Very robust	Individuals who are robust, active, energetic and motivated, they commonly exercise regularly, and are among the fittest for their age.
2 - Robust	Individuals who have no active disease, symptoms but are less fit than those in category one; often they exercise or are very active occasionally.
3 - Managing Well	Individuals whose medical problems are well controlled, but are not regularly active beyond routine walking.
4 - Vulnerable	While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.
5 - Mildly Frail	These individuals often have more evident slowing and need help in high orders (finances, medication, transportation, heavy housework).
6 - Moderately Frail	Individuals need help with all outdoor activities. Indoors they need help with housekeeping, and often have problems with stairs. They also need help with bathing and might need minimal assistance with dressing.
7 - Severely Frail	Completely dependent for personal care, from either cause (physical or cognitive). Even so, they seem stable and not at high risk of dying.
8 - Very Severely Frail	Completely dependent, and approaching the end of life (within 6 months).
9 - Terminally ill	Approaching the end of life. This category applies to any people with a life expectancy <6 months, who are not otherwise evidently frail.
If dementia is present, the degree of frailty usually corresponds to the degree of dementia. • **Mild dementia**: includes forgetting the details of a recent events though still remembering the event itself, repeating the same question/story and social withdrawal • **Moderate dementia**: recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting • **Severe dementia**: they cannot take care of themselves without help	

Table 2: Clinical frailty scale criteria.

Conversely, chronic kidney disease (CKD) patients can present any value and deterioration rate of their GFR, showing at least some of the following alterations, such as: high serum urea, creatinine, phosphorus, parathyroid hormone levels, and/or low serum hemoglobin, calcium, vitamin D levels, significant proteinuria, hematuria, and/or abnormal renal ultrasound [1]. Additionally, successful renal ageing has all the characteristics of normal renal ageing expect for not

presenting or presenting minimally (<1 ml/min since 40 years) the age-related GFR reduction. Therefore, three categories of successful renal ageing have been proposed based on the degree of GFR and renal reserve preservation (Table 3) [3].

Categories	Age (years)	GFR and RR
Level I	> 65	> 65 ml/min/1.72 m^2 and preserved RR (at least 20%)
Level II	65-79	65-50 ml/min/1.72 m^2
Level III	≥ 80	49-30 ml/min/1.72 m^2
GFR: Glomerular Filtration Rate, RR: Renal Reserve		

Table 3: Renal successful ageing classification.

Finally, CKD prevalence increases with age, and can even overlap with frailty status (senescence). Frail individuals tend to progress to end-stage renal disease and have higher rates of mortality, whereas patients with advanced stages of CKD are more likely to become frail. Additionally, this subgroup of CKD frail patients has more clinical complications, therapy needs and worse overall prognosis. Thus, the combination of CKD and frailty has been recognized as a different syndrome named senescent nephropathy (Table 4) [2,5].

It is worth pointing out that diagnosing senescent nephropathy implies treating not only patient´s CKD but also his/her frailty, which requires a team intervention, including nurses, occupational therapists, physiotherapists, physicians, psychologists, pharmacists, speech therapists, and social workers [10]. Since frailty is considered a dynamic syndrome consisting of a continuum from robust status to severe frailty, there is a considerable 'interventional window' in order to perform a therapeutic intervention which could potentially achieve a total or partial syndrome reversal. Frailty therapeutic strategies are mainly based on the prescription of rehabilitation, low-intensity resistance and aerobic exercise, adequate caloric and protein intake, vitamin supplementation, and avoidance of polypharmacy [4].

Senescence and chronic heart disease

It has been documented that heart rate and sinoartrial node function decline with age, although not at the same rate in all elderly individuals [10]. In addition, Moghtadaei et al. have reported that frailty strongly correlates with heart rate and sinoauricular node functional decline, independently from the patient´s chronological age [11,12]. Their study quantified frailty in young and aged mice using a non-invasive frailty index, which was defined as a combined score on health deficits and divided by 31 non-invasive measurements that report age-associated adverse outcomes. Changes in sinoauricular node function, electrical conduction, action potential morphology and fibrosis were highly correlated with, and graded by frailty score [11,12].

The prevalence of frailty among chronic heart failure (CHF) patients varies depending on the population

characteristics and the assessment tools used. Most studies have reported a high prevalence of frailty among patients with chronic heart failure.

	Normal renal ageing	Successful renal ageing	CKD (any stage)	SN
GFR	low (expected value for age)	normal	any value	any value
Serum urea	normal	normal	normal / high	normal / high
Serum creatinine	normal	normal	normal / high	normal / high
Hematocrit	normal	normal	normal / low	normal / low
Parathyroid hormone	normal	normal	normal - high	normal - high
Urinalysis	normal	normal	normal / altered	normal / altered
Renal image	normal	normal	normal / abnormal	normal / abnormal
Clinical functional status	robust / frail	robust / frail	robust	frail
Treatment	none	none	nephroprevention	nephroprevention rehabilitation
GFR: glomerular filtration rate; SN: Senescent nephropathy				

Table 4: Clinical comparison among different renal ageing and chronic kidney disease (CKD).

Besides, when frailty was evaluated using a comprehensive geriatric assessment method, the prevalence was higher than when assessed by Fried frailty phenotype score. Higher frailty prevalence was identified among female aged population, who typically presents with a heart failure with preserved ejection fraction and high comorbidity burden [10]. There is a considerable overlap between frailty and CHF, increasing each of these conditions the incidence and prevalence of the other, therefore a common pathophysiological pathway can be involved. Frail CHF patients are more likely to have higher rates of morbidity, hospitalization and mortality, and frailty evaluation can identify CHF vulnerable patients, and assess their cardiosurgical risk [10]. Since chronological age per se does not properly reflect heath status, identifying the "biologically aged" by performing a frailty evaluation could help to distinguish the presence of conventional cardiopathy from senescent cardiopathy (cardiopathy + pathologic ageing) in order to differentiate between these conditions since they have different prognosis and therapeutic strategies.

Senescence and chronic lung disease

In the Cardiovascular Health Study, frailty and respiratory impairment (airflow limitation or restrictive pattern) were strongly associated between each other and substantially increase mortality when both are present [13]. The impact of lung disease and frailty on respiratory function and mortality appears to be synergistic. Therefore, it seems that frailty and chronic respiratory disease (CRD) could share the same underlying mechanisms of progression [9]. Gait speed test is a consistent predictor of adverse outcome in community-dwelling patients with chronic obstructive pulmonary disease (COPD), and can predict the risk of readmission in hospitalized patients with this condition. Even, gait speed can predict mortality in patients suffering from severe COPD. Therefore, gait speed test or pulmonary function tests could both be used to evaluate frail CRD patients as independent markers for their disease severity and therapy outcomes [13]. Despite the documented correlation between frailty and CRD represents a valuable but underestimated approach, frailty phenotype can identified a poor outcome risk factor even in younger adults [9,13]. Since frailty is relatively frequent among CRD elderly patients and is independently associated with more frequent exacerbations of lung disease, all-cause hospitalization, disability, falls, poor health-related quality life, and all-cause mortality; patient´s frailty assessment could help to distinguish conventional CRD from senescent neuropathy (CRD + pathologic ageing), aiding to distinguish their different prognosis and therefore leading to perform their different therapies.

In conclusion, based on the exposed above it is crucial that current clinical research determines how to differentiate normal ageing from chronic disease in each organ of the human organism in order not to confuse normal ageing with disease, and consequently to avoid chronic disease over diagnoses and treatment. In addition, it is also crucial to evaluate frailty phenotype in every patient, independently of his/her age, who suffers from an organ chronic disease which could has systemic impact (kidney, heart, lung, brain, etc.) in order to distinguish chronic disease from its senescent form since they could have different prognosis, as well as diagnostic tests and therapeutic requirements.

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