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Special Issue

The Human Capital of Age

Guest Editors

Natale Gaspare De Santo, Luigi Santini, Vincenzo Bonavita



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High fish consumption decreased the likelihood of depressive symptoms in community-living older people: a randomized-controlled trial

A. Shapouri-Moghaddam¹, M. Bagherniya², S.-M. Ehteshamfar³, H. Rahimi⁴, M. Safarian²

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Background and aims. This study was an attempt to examine the interventional relationship between regular fish consumption and depression among the elderly, Mashhad, Iran.

Methods. A total of 96 adults who aged 60 years or over was recruited and then divided into groups A and B. The subjects' initial eligibility was tested using Beck Depression Inventory (BDI). Group A received fish four times a week whereas their peers in group B consumed fish two or fewer times per week. The outcome measures were 12-item general health questionnaire (GHQ-12) and 15-item Geriatric Depression scale (GDS-15).

Results. The results indicated that GHQ and GDS scores decreased non-considerably following three-month intervention. Fish consumption was associated with a lower likelihood of depression (dichotomized GDS: OR[odds ratio] = 0.73, 95% CI[confidence interval] = 0.28-1.87, $p = 0.618$; dichotomized GHQ: OR = 0.67, 95% CI = 0.26-1.73; $p = 0.334$).

Conclusions. It could be concluded that diet supplementation of the elderly with fish decreased the likelihood of depressive symptoms. However, this improvement was not statistically significant.

Key words: Older adults, Interventional study, Fishes, Randomized controlled trial, Depression

INTRODUCTION

Depressive disorders are considered as a chronic or episodic condition in adolescence or early adulthood, being typically recurrent and comorbid with addiction or other mental and physical illnesses¹. It was revealed that 17-20% of the general population are affected by mild to severe depression, with approximately 5% of adults experiencing severe depression². Nevertheless, these figures differ from country to country, for example in Iran 36.7%³⁻⁵.

Given the growing life expectancy across the globe, Iran in particular, the elderly population is on the rise at unprecedented pace; thus prevalence of depressive disorders is more likely to increase remarkably^{6,7}. A few

studies have addressed outcomes and predictors of depression in later life. In this regard, some have reported no predictors⁸. However, advanced age may play an important role in development of depression among older adults^{9,10}.

Insufficient diet is one of the key features related to depression, which may cause other chronic disease, such as type 2 diabetes mellitus¹¹. On the other hand, omega-3 polyunsaturated fatty acids (PUFA) have shown positive contribution to the progress and treatment of late-life depression^{12,13}.

It is frequently reported that fish is considered as an indispensable component of a healthy dietary pattern. A number of observational studies (cross-sectional and cohort) have supported the great impact of fish

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consumption on the management of certain non-transmissible or psychiatric diseases, including cardiovascular disorders, Alzheimer's disease, rheumatoid arthritis, diabetes, cancer, and so forth¹⁴⁻¹⁷.

There exists emerging evidence that confirms the contribution of fish and fish oils to mental health. Several cross-sectional studies have demonstrated that the lower rates of depression in Greek islands may correspond with high fish intake^{18,19}. Some have found no correlation between fish consumption and depression though^{20,21}.

Iran with several ethnicities has undergone profound socioeconomic shifts over the past three decades, which, in the long run, have affected lifestyle, health, and accordingly prevalence of depressive diseases²². Moreover, there is a large gap between present fish consumption and the amounts for nutritional goal (twice per week) in Iran²³. Given lack of sufficient randomized controlled trials, status of present fish consumption and different lifestyles in Iranian aging adults, this study was intended to investigate the effectiveness of high fish consumption on the management of depressive symptoms using a randomized controlled trial among community-living older adults in Iran.

MATERIAL AND METHODS

STUDY DESIGN

This study was considered as a randomized controlled trial of three months duration, aiming to assess the impact of fish consumption on the treatment of depression. Accordingly, 96 participants were enrolled from residents of a senior housing complex, Mashhad, Iran. The recruitment was carried out from October 2011 to August 2013. The subject's initial eligibility was evaluated based on the Beck Depression Inventory (BDI). The original BDI with 21 items concerning the subject's condition in the previous week was used in this trial. It was translated into Persian language and validated for clinical applications²⁴. Then, they were randomly assigned into groups A (high fish consumption; four times a week) and B (control condition; two or fewer times per week). Moreover, pre- and post-test scores of depression were obtained using the 15-item Geriatric Depression scale (GDS-15) and 12-item general health questionnaire (GHQ). Therefore, the outcome measures included changes in depression symptoms through the GHQ and GDS.

INCLUSION CRITERIA

Three eligibility criteria – being 60 years old or over (at the time of assessment), being able to provide informed consent, and gaining score 24 or over on the

Mini-Mental State Examination (MMSE) – were adopted to select the target population. If participants were on any psychological therapies or antidepressant medication, they were allowed to adhere to the treatment regimen for at least fortnight prior to initiation of the study. Furthermore, it was mandated that each participant must not leave the institution for more than one week during the intervention period and be physically able to eat foods as prescribed.

EXCLUSION CRITERIA

Participants with any known psychological and severe medical conditions (bipolar I or II disorder, food allergies, personality disorder) were excluded from the study.

STUDY INTERVENTION

Initially, a number of 140 cases were recruited from the institution. With 15% attrition over three months, the ultimate desired sample size resulted in 96 participants. Participants were divided into groups A ($n = 54$) with 480 g/week of trout fish and B ($n = 42$), which was provided with the less frequent fish-based diet. The subject's common diet was actually replaced by fish so that no changes occurred in their caloric intake over three months. In this regard, all the study groups were to consume specified amounts of food according to the nutritional material combination chart (consisting of 700 different foods issued by Iranian Institute of Nutrition). Moreover, their weight was continuously measured to adjust the caloric intake. The procedure and data collection were conducted by the study nurses who were blinded to the group allocation and were not involved in the usual clinical care of the institution. Due to the small number of the participants, randomization was carried out using random number tables.

OUTCOME MEASURES

The GDS and GHQ were administered to the study groups in order to determine changes in the mean score of depressive symptoms at three months. The following baseline variables were collected via demographic questionnaire: age, sex, smoking status, BMI, marital status, physical activity, educational level, and disease prevalence. The GHQ-12 is another questionnaire used in this study to screen mental health. It was proved to have good reliability and validity in Iranian population²⁵. Cut-off point ≥ 5 denotes the presence of depressive symptoms in older adults (Costa et al., 2006). The Iranian version of the GDS-15 was developed by Malakouti et al. with the optimum cutoff score of 7/8²⁶.

STUDY INTEGRITY

The present study was approved by the Medical Research Committee affiliated to Mashhad University of

Medical Sciences, Mashhad, Iran. We obtained written informed consent from all the elderly. Moreover, the CONSORT guidelines were adopted to develop the study.

DATA ANALYSES

In analysis phase, a researcher blinded to the treatment conditions conducted data processing on triplicated measures. The Mann Whitney U test was performed to determine differences between the two groups' GDS and GHQ scores (in both continuous and dichotomized forms) at three months. Adjustment for confounders was carried out through ANCOVA. In order to investigate the association of fish consumption with the improvement of depressive symptoms (GDS < 5 and GHQ < 5), four models were developed through multiple logistic regression. Models 1, 2, 3, and 4 were respectively adjusted for four categories including demographics, lifestyle, health condition, and MMSE scores. All statistical tests were considered significant at an alpha level of 0.05 with 95% confidence intervals.

RESULTS

Of 140 eligible subjects in the institution, 96 met the inclusion criteria, randomized to either a control ($n = 42$) or a case ($n = 54$) group, and completed the dietary intervention of three-month duration. As indicated in Table I, both groups were comparable across a range of confounders ($p > 0.05$). However, there was a notable difference in disease prevalence between the two groups ($p < 0.05$).

The mean (SD) GDS scores at baseline in the case and control groups were 3.67(2.08) and 4.05(1.77), respectively. Following three months when the diet program completed, these values approximately resulted in 2.83(1.99) and 3.31(1.54), respectively. The result of GDS scores presented no statistically significant difference between the study groups ($p > 0.05$). The GHQ scores were similarly improved non-considerably ($p > 0.05$) (Tab. II). Even following adjustment for age, gender, and baseline values, the difference in the scores of GDS (0.17%) and GHQ (0.37) between groups A and B was not remarkable at the end of three months ($p > 0.05$).

Comparison of dichotomized GDS and GHQ scores less than 5 between the study groups was summarized in Table III. The proportions of the elderly obtaining GDS < 5 or GHQ < 5 at three month were 75.92% or 77.78% (group A) vs 71.43% or 69.04% (group B), respectively. Likewise, the dichotomous outcomes were higher in the case group in comparison with the control group ($p > 0.05$). Therefore, the influence of high fish consumption did not significantly change the dichotomized scores of depression even if adjusted for age and gender (multiple adjusted odds ratio of scoring GDS < 5 = 0.73, 95% CI: 0.28-1.87). The OR gained from GHQ < 5 established on the first adjusted model in group A was approximately 67% that of group B (Tab. II). Furthermore, the OR based on models 2, 3, and 4 revealed that adjustment for other confounders did not notably change this finding (data not shown). This also was indicative of an inverse connection between high fish consumption and the scores of depression.

Table I. Baseline characteristics of the participating adults at enrolment.

Variables	Group A N = 54	Group B N = 42	p-value
Mean age (SD)	66.31 (5.11)	66.81 (5.62)	0.876
Mean BMI (SD)	21.06 (3.50)	23.50 (4.10)	0.102
Males (%)	23 (42.59)	26 (61.90)	0.060
Education level (primary or lower) (%)	34 (62.96)	25 (59.52)	0.731
Marital status (%)			
Single	13 (24.07)	14 (33.33)	0.562
Married	12 (22.22)	7 (16.67)	
Other (separated, divorced, widowed)	29 (53.70)	21 (50.00)	
Smoking (%)	16 (29.63)	15 (35.71)	0.527
Exercises over once a week (%)	28 (51.85)	21 (50.00)	0.857
Disease prevalence (%)			
Hypertension	30 (55.56)	12 (28.57)	0.041
Diabetes	16 (29.63)	16 (38.10)	
Heart failure	3 (5.56)	7 (16.67)	
Stroke	5 (9.26)	7 (16.67)	
Mean MMSE score (SD)	27.00 (1.69)	26.81 (1.57)	0.614

Table II. GDS and GHQ total scores (continuous outcomes) at baseline and three months and adjusted differences between the two groups at three months.

Variable		Result by study group			Comparison between groups A and B
		Group A	Group B	p-value	Difference in means (95% CI) ^b
Mean GDS score (SD)	Baseline	3.67 (2.08)	4.05 (1.77)	0.247	-0.17 (-0.48 to 0.15)
	3 months	2.83 (1.99)	3.31 (1.54)	0.068a 0.295b	
Mean GHQ score (SD)	Baseline	4.11 (2.32)	4.26 (2.13)	0.678	-0.37 (-0.75 to -0.00)
	3 months	2.93 (2.13)	3.48 (2.07)	0.133 ^a 0.051 ^b	

^a Mann-Whitney U; ^b ANCOVA adjusting for age, gender, and baseline measures

DISCUSSION

Along with increased incidence of late-life depression, the consumption of fatty acids either from animal or plant sources has diminished in older populations²⁷. Much more attention has drawn to a relationship between fish consumption and depression in aging people. The present study showed an interventional relationship between high fish consumption and depressive symptoms in aging adults; in other words, multiaadjusted analysis demonstrated that greater consumption of fish reduced the odds of developing depression (around 70% likelihood vs the control) founded on the GDS-15 and GHQ-12 after controlling across a range of behavioral and sociodemographic characteristics. This finding was confirmed by other scholars whose studies exhibited an inverse association of fish consumption with depressive symptoms in community-living seniors^{11 19 28}. However, there has some conflicting evidence against the correlation between fish intake and depressive symptomatology among the middle aged and elderly^{20 21 29}. This might be explained by the effect of confounders namely demographics, regional factors, personality, socioeconomic level, income status, ethnic/cultural identity, occupation, dispositional optimism and so forth³⁰. Indeed, it was indicated that bereavement, sleep disturbances, disability, previous depression, and gender account for risk factors of depression³¹. The large 10/66 study showed that the association

between fish intake and depression among the elderly considerably differed from one nation to another with various incomes²⁰. Moreover, male Melbourne Chinese and Caucasian presented different levels of platelet phospholipids n-3 PUFA³². This implies that ethnic and demographic factors play a pivotal role in the interplay of diet and depression. In this regard, high-fish consumption was merely linked to decreased likelihood of depressive symptoms in European descent however several population-based studies in North America, South America, Asia, and Oceania failed to observe such association³³.

Of all different dietary habits, the greatest fish consumption was observed in individuals with no or low depressive symptoms and *vice versa*^{34 35}. In a similar way, a deficit in omega-3 PUFAs leads to depression^{36 37}. Martin, for example, showed that an inadequate amount of omega-3 PUFAs may cause a higher frequency of depressive disorders³⁶. Some studies have indicated the contribution of omega-3 fatty acids intake to the management of depression and concluded that the content of phospholipids PUFAs in human tissues acts as an antidepressant during adulthood³⁸⁻⁴⁰. On the other hand, a lack of omega-3 PUFAs causes different medical conditions such as some types of cancer, and neurological, cardiovascular, autoimmune and metabolic diseases. Furthermore, an interventional association has been reported between intakes of omega-3 fatty acids from fish and a decrease in atherosclerotic process.

Table III. GDS <7 and GHQ <5 (dichotomous outcomes) as well as odds ratio for group A vs. group B with 95% confidence intervals.

Variable		Result by study group			Comparison between Groups A and B
		Group A	Group B	p-value ^a	Odds ratio (95% CI) ^b
GDS < 7	3 months	41 (75.92)	30 (71.43)	0.618	0.73 (0.28 to 1.87)
GHQ < 5	3 months	42 (77.78)	29 (69.04)	0.334	0.67 (0.26 to 1.73)

^a Chi squared test; ^b model adjusted for age and gender.

Of omega-3 PUFAs, docosahexanoic acid and eicosapentaenoic acid are highly related to the etiology of depression⁴¹. An abnormal metabolism of omega-3 long chain-PUFAs was connected to depression. Additionally, fish consumption and changes in fatty acids were shown to have a relationship with the inflammatory response. The consumption of fish more than 150 g per week attenuated levels of proinflammatory markers⁴², which, in turn, have positive impacts on depressive symptomatology⁴³.

Strengths of this investigation regard the design of the study where two validated instruments were used to measure outcomes. Furthermore, control over confounders using a randomized controlled trial among community-living older adults was reduced the potential of recall bias. The present study lacks screening tools based on somatic symptoms.

In conclusion, the population of older people is on the rise across the globe and they still stand in need of more attention due to the spread of late-life depression. Concerning the influence of national and cultural parameters, this study was developed to examine the association between fish consumption and depression among Iranian older adults. It was indicated that there was an inverse connection between high fish consumption and the presence of depression symptoms. Therefore, the higher consumption of fishes as rich source of omega-3 fatty acids is useful for the treatment and management of depressive diseases. However, this improvement was not statistically significant.

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The implementation of a geriatric patients blood management program to monitor hemoglobin level in nursing homes

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Background and aims. In reference to the Resolution WHA63.12 of 21/05/2010 from the World Health Organization, the Italian National Blood Center has promoted an initiative encapsulated by the term Patient Blood Management (PBM). The aim of this study is to examine the relationships among the prevalence of genera-age-associated risk factors of anemia and hemoglobin level in geriatric patients with cognitive decline through CBA SIPCARplus software (medical records). Before this implementation, there was not the traditional blood management program in nursing homes.

Methods. The CBA database has been developed by a dedicated working group using Delphi process and PBM. It contains records on patient characteristics, and one set of biomarker laboratory.

Results. Between 2014 and 2015, 283 geriatric patients were enrolled at three Italian elderly nursing homes. Among these patients, 14% were men and 86% were women (mean age 79 years) and the overall prevalence of anemia was 55.9%; 32.6% of the geriatric patients were at risk of malnutrition and 11.5% were malnourished. Multivariate analysis determined that comorbidity was highly associated with malnutrition risk measured by Malnutrition Universal Screening Tool ≥ 2 , cognitive decline measured by Mini-mental State Examination ≤ 19 , functional independence in two or more basic activities of daily living, Hgb level of 69 g/L ($p = 0.01$) and Hgb level of 100 g/L ($p = 0.02$). Two variables were significantly associated with an increase of the transfusion threshold above 90 g/L: the poor tolerance of anemia ($p = 0.001$) and clinical risk situations ($p = 0.03$).

Conclusions. The appropriateness of results could be useful to better describe the role of PBM with CBA and biomarkers recorded in geriatric practice, transfusion thresholds, target hemoglobin levels after transfusion.

Key words: Anemia, Patient Blood Management, CBA outcome set, Cumulative Illness Rating Scale, Nursing Home

ABBREVIATIONS

WHA: World Health Organization
PBM: Patient Blood Management
CBA: Social Health Folder
CIRS: Cumulative Illness Rating Scale
CRS: Crichton Rating Scale
MUST: Malnutrition Universal Screening Tool
MMSE: Mini-mental State Examination
CI: Confidence interval
CrCl: Creatinine Clearance
CGA: Comprehensive geriatric assessment
MLF: Multidimensional loss of function

INTRODUCTION

In reference to the Resolution WHA63.12 of 21/05/2010 from the World Health Organization, the Italian National Blood Center has promoted an initiative aimed at systematizing innovative and more effective methods and instruments for ensuring appropriate organizational and clinical management of blood use¹. This initiative is a ground-breaking multiprofessional, multidisciplinary and multimodal project encapsulated by the term Patient Blood Management (PBM) and Geriatric anemia. Anemia in the elderly (defined as people aged > 65

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years) is common and increasing as the population grows. In older patients, anemia of any degree contributes significantly to morbidity and mortality and has a significant effect on the quality of life. Despite its clinical importance, anemia in the elderly is under-recognized and evidence-based guidelines on its management are lacking².

Causes of anemia in the elderly are divided into three broad groups: nutritional deficiency, anemia of chronic disease (ACD) and unexplained anemia (UA). These groups are not, however, mutually exclusive. In any given patient, several causes may co-exist and may each contribute independently to the anemia.

Other causes like Cancer or hematological malignancy related anemia were investigated for renal failure and/or inflammation (myelodysplastic syndromes, chronic leukemia or lymphoma and sarcopenia). Both types may cause anemia, mainly via erythropoiesis inhibition by cytokines, although the mechanisms of inflammatory anemia are incompletely elucidated. As a result, protracted elevation of interleukin (IL)-6 and tumor necrosis factor (TNF)- α in the plasma of elderly patients after exposure to inflammatory stimuli can be seen. This may be a common mechanism for the production of anemia in chronic illness unique to elderly patients³.

Another approach is based on the definition of Hb concentrations that are optimal for the clinical outcome of elderly subjects⁴.

Anemia of the elderly gives a challenge and a burden to them, the community, and the health care providers. All healthcare providers should be aware that anemia impacts a significant group within our societies. It is an entity that lies within our ability to diagnose and treat with PBM.

PBM is a holistic approach to the management of blood as a resource for each, single patient; it is a multimodal strategy that is implemented through the use of a set of techniques that can be applied to individual cases⁵. Indeed, the overall outcome resulting from the implementation of PBM cannot be fully appreciated and explained simply by summing up the effects of the single strategies and techniques used, since these can only produce the expected optimal outcome if used in combination⁶. PBM is, therefore, a patient-centered and multidisciplinary project which involves Hematology, Geriatrics, Physiotherapists, Nurses or just primary care.

It is, also, a multimodal approach to the optimal management of anemia and haemostasis, to limiting allogeneic transfusion needs, and to use the blood components appropriately and, when relevant, plasmaderived medicinal products⁷.

The concept of PBM is not centered on a specific pathology or procedure, nor on a specific discipline or sector of medicine, but is aimed at managing a resource,

“the patient’s blood”, shifting attention from the blood component to the patient who, therefore, acquires a central and preeminent role⁸.

PBM combines the dual purposes of improving the outcomes of patients and reducing costs, being based on the patient rather than on allogeneic blood as the resource. For this reason, PBM goes beyond the concept of appropriate use of blood components and plasma-derived medicinal products, since its purpose is to avoid or significantly reduce their use, managing, in good time, all the modifiable risk factors that can lead to the need for transfusion⁹.

These aims can be achieved through the so-called “three pillars of PBM”, which are crucial for making the paradigmatic shift that characterizes the innovative, patient-centered approach: (i) optimizing the patient’s erythropoiesis; (ii) minimizing bleeding; and (iii) optimizing and exploiting an individual’s physiological reserve to tolerate anemia. Each of these three key points are a strategic response to clinical circumstances that can cause adverse outcomes and necessitate the use of allogeneic transfusion therapy, namely anaemia, blood loss and hypoxia, respectively¹⁰.

PBM is, therefore, intended to guarantee all patients a series of personalized programs, based on clinical requirements and the characteristics of the patients themselves, with the dual purposes of using allogeneic transfusion support appropriately and reducing the need for this resource. For this reason, PBM requires multidisciplinary and multimodal strategies to systematically identify, evaluate and manage anemia (boosting, if necessary, individual physiological reserves) and to avoid or minimize blood losses. It seems necessary to produce specific national standards¹¹.

The aim of this study is to examine the relationships among the prevalence of genera-age-associated risk factors of anemia and hemoglobin level in geriatric patients with cognitive decline through CBA SIPCARplus (medical records).

Before this implementation, there was not a traditional blood management program to evaluate risk factors of anemia and hemoglobin concentration associated with age and sex. It used a protocol for massive bleeding without monitoring the prevention of risks in this structured way.

MATERIALS

The CBA database has been developed by a dedicated working group using Delphi process and PBM.

It contains records on patient characteristics called health-assessment-delivery-warnings-analysis area, and one set of biomarker laboratory data identified in several variables

(the hemoglobin level, iron, ferritin, transferrin saturation, folate, vitamin B12, C-reactive protein, thyroid-stimulating hormone-TSH, albumin, and haptoglobin). It was categorized into normal and abnormal values according to standard laboratory norms.

The three pillars of the PBM with CBA are:

- 1) Optimization of erythropoiesis: detect anemia; identify and treat its underlying causes; re-evaluate the patient, if necessary; treat iron deficiency and iron-deficiency anemia, anemia of chronic disease and functional iron deficiencies, so-called ironrestricted erythropoiesis; treat deficiencies of other haematinics;
- 2) Minimization of blood losses: identify and manage bleeding risk, minimize iatrogenic bleeding, plan the procedure carefully and prepare well in very selected cases;
- 3) Optimization of the tolerance of anemia: assess and optimize the patient's physiological reserve to tolerate anemia and risk factors; compare estimated blood loss with the individual patient's tolerable blood loss; formulate a personalized blood management program that includes patient specific blood-conservation techniques; adopt restrictive blood transfusion thresholds.

Descriptive and inferential statistics were applied to describe and compare patients' demographic and epidemiological characteristics in Nursing Home. The IBM SPSS version 21 statistical software was used to perform data analysis. The data analysis was concluded in January 2014.

METHODS

Researchers responsible for recruitment from three nursing homes informed management and potential participants about the study. Inclusion criteria were as follows: age, availability of a venous blood sample result including hemoglobin (Hb) concentration collected during the current nursing home stay, possibility of verbal communication with the patient or a proxy, and informed consent to participate by the patient or legal guardian.

Exclusion criteria were as follows: non-correctable visual or hearing impairment, severe pain, sedation, or clinical depression. Blood samples were taken for laboratory biomarker assays of Hb level, iron, ferritin, transferrin saturation, folate, vitamin B12, C-reactive protein, TSH, albumin, and haptoglobin.

The comprehensive geriatric assessment (CGA) for this study consisted of six tools and their ranking methodologies to evaluate the following functional domains: cognition, mobility, transfer skills, competence in

performing basic activities of daily living (BADLs), and swallowing ability¹².

The Barthel Index (BI) assesses BADL functionality using a rating scale from 0 (totally dependent) to 100 (maximal independence). An abnormal outcome was defined as 90 points or less¹³. The mini mental state examination (MMSE) measures the global cognitive state with a rating ranging from 0 (severe cognitive impairment) to 30 (normal cognitive function)¹⁴. Results of 27 points or less were considered abnormal. The clock-drawing test (CDT) covers cognitive domains incompletely tested for by the MMSE, such as executive function and spatial visualization skills. It uses a scale from 1 (perfect) to 6 (no reasonable representation of a clock), with a result of 3 or higher rated as abnormal. The timed up and go (TUG) test was used to assess mobility status. For methodical reasons, it uses five ranks according to the time needed to finish the test: ≤ 15 s, 1; > 15 to ≤ 25 s, 2; > 25 to ≤ 35 s, 3; > 35 s, 4; and TUG test not realizable, 5. Results of 3 or higher were considered abnormal. The Esslinger Transfer Scale (ETS) refers to the degree of independence while changing position in bed and transferring oneself from bed to chair, and it ranges from 0 (no assistance needed) to 4 (more than one professional assistant required). Ranks from 2 upwards were regarded as a functional limitation. Daniels test was used to detect dysphagia and was rated abnormal (positive) or normal. Multidimensional loss of function (MLF) as an aggregated outcome was diagnosed when three or more CGA tests showed an abnormal result¹⁵. In order to adjust for possible confounding factors in the relationship between anemia and MLF, this study collected information on 12 major comorbidities directly from patients by studying their medical histories. Renal and thyroid functions were assessed on the basis of laboratory results: serum creatinine concentration with a standard of 0.5-0.9 mg/dL in women and 0.5-1.1 mg/dL in men, and TSH with a standard of 0.27 and 4.20 μ U/mL, respectively). Multimorbidity was defined as the non-specific presence of more than one major disease¹⁶.

This study was approved by the Internal Review Board of the university hospital, Bergamo. Informed consent was procured, and the protection and confidentiality of data was guaranteed according to applicable privacy laws.

RESULTS

Epidemiological studies consistently show an increase in the prevalence of anemia with advancing age, despite differences across studies in patient characteristics such as age and comorbidities¹⁷.

Perhaps of greater significance, anemia has been

shown to impact mortality in elderly patients with other co-morbid conditions. For example, Esekowitz and colleagues have shown an increase in mortality in elderly patients with congestive heart failure as compared with their non-anemic cohorts¹⁸.

Improvement in hemoglobin levels can also lead to improvements in end-organ function. Hayashi and colleagues have shown that the left ventricular function improves in chronic renal failure patients treated with erythropoietin. These data begin to address the important question of the relative roles of the anemia and the co-morbid condition in the excess morbidity and mortality experienced by the anemic elderly¹⁹.

In this study 283 geriatric patients at three Italian nursing homes for the elderly were enrolled during 2014 and 2015. The mean age of enrolled patients was 79 years, with 14% male and 86% female. The overall prevalence of anemia was 55.9%. 32.6% of patients were at risk for malnutrition and 11.5% were malnourished. Comorbidities were weighed with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) ≥ 4 ²⁰ (Figg. 1-2).

The mean total CIRS-G score was 9 ± 3.7 and the mean composite CIRS-G score was 3.7 ± 1.5 (Fig. 3). The mean Creatinine Clearance (CrCl) was 40.9 ± 16.5 mL/min (Normal values was: 56 to 131 mL/min). The mean Hb level was 122 g/L. The Hb level was < 120 g/L in 110 (61.1%) patients and ≥ 120 g/L in 173 (38.9%) patients. In the group with severe anemia, the mean Hb level was 105 ± 11 g/L²¹.

Anemia was multifactorial in most patients: the mean number of potential causes per patient was 1.85 ± 1 , and 65.4% of patients had two to four concomitant causes^{22,23}. Anemia prevalence was 2.12-fold higher in patients at risk for malnutrition than the malnourished groups. When the study compared age, sex, CrCl, and comorbidity scores in the groups with and without anemia, the total CIRS-G score was the only variable significantly and independently associated with anemia ($p < 0.001$)²⁴. The total CIRS-G score was also the only variable significantly associated with the Hb level in the multivariate analysis ($p < 0.001$). Multivariate analysis determined that comorbidity was highly associated with malnutrition risk as measured by the Malnutrition Universal Screening Tool ≥ 2 (Fig. 4); cognitive decline as measured by the MMSE ≤ 19 ; functional dependence in two or more basic activities of daily living; Hb level of 69 g/L ($p = 0.01$); and Hb level of 100 g/L ($p = 0.02$) (Tab. I).

Overall, 61% of patients were presented with three or more abnormal results in the six tests of the CGA and were thus diagnosed with MLF. Logistic regression identified a significant association of both anemia and low Hb concentrations with abnormal outcomes in five tests of the CGA and therefore with functional deficits

Table I. Multivariate Analyses of Geriatric test score, comorbidity score and biomarkers laboratory.

Comorbidity	MUST ≥ 2 p	MMSE ≤ 19 p	Barthel Index ≤ 50 p
Hb>69 g/L_cod	0.105	0.013	0.001
Hb>100 g/L_cod	0.035	0.021	0.194
CIRS_SCORE ≥ 4	0.495	0.029	0.535

Test score: MUST, MMSE, Barthel Index; biomarkers laboratory Anemia severity: Hb > 69 g/L, Hb > 100 g/L; comorbidity: CIRS_SCORE ≥ 4 .

like mobility limitation, impaired cognition, and dysphagia. Furthermore, being anemic increased the odds of MLF more than fourfold²⁵. The significance of this relationship persisted after adjustment for various major comorbidities.

Given the association of anemia with MLF, Hb level might serve as a useful geriatric screening marker to identify frail older people at risk for adverse outcomes; such a screening should contain indicators of functional deterioration²⁶.

This study also evaluated anemia treatment to gain insights into Hb threshold for transfusion²⁷.

The mean hemoglobin level before red blood cell transfusion was 84.5 ± 9.4 g/L. There was a significant inverse relationship between the baseline Hb and the Hb response to treatment ($p = 0.007$) [28]. Hb loss after treatment decreased from 38 (29-49) g/L at baseline to 31 (26-40) g/L after algorithm implementation ($p < 0.001$). The mean number of red blood cell units prescribed for each transfusion was 1.88 ± 0.55 , with the only predictive factor being the hemoglobin level ($p < 0.001$). Two variables were significantly associated with an increase of the transfusion threshold above 90 g/L: the poor tolerance of anemia ($p = 0.001$) and the clinical situations at risk for poor tolerance of anemia ($p = 0.03$)²⁹. The most frequent symptoms of poor tolerance of anemia were cardiovascular symptoms and acute neuropsychiatric symptoms that could be considered as specific criteria for red cell transfusion in the elderly³⁰.


DISCUSSION

The results confirm that anemia is prevalent and often multifactorial in the elderly: 55.9% of study participants were anemic and 65.4% of anemic patients had two to four concomitant potential causes of anemia. Anemia increases the risk of mortality and morbidity and adversely affects quality of life, self-sufficiency, and cognitive function³¹.

This study showed that low Hb levels were associated

Cumulative Illness Rating Scale for Geriatrics
CIRS-G online calculator

Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, et al.
"Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale"
Psychiatry Res. 1992 Mar;41(3):237-48.



I→Comorbidities are diseases or disorders that coexist with a disease of interest. Initially developed by Linn et al., the CIRS was later revised by Miller et al. to reflect common problems of the elderly. They renamed the index "Cumulative Illness Rating scale for Geriatrics", commonly abbreviated CIRS-G. This scoring system measures the chronic medical illness ("morbidity") burden while taking into consideration the severity of chronic diseases in 14 items representing individual body systems.

The general rules for severity rating are:

- 0→No problem affecting that system.
- 1→Current mild problem or past significant problem.
- 2→Moderate disability or morbidity and/or requires first line therapy.
- 3→Severe problem and/or constant and significant disability and/or hard to control chronic problems.
- 4→Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

The cumulative final score can vary theoretically vary from 0 to 56 (although a very high score is impossible).

Total Score: **24** (max.52)
CIRS-G Severity Index: **1.7** (max.4)

Guidelines II

Please rate each of the following individual body system

	0	1	2	3	4
Cardiac	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Vascular	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hematological	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Respiratory	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ophthalmological and ORL	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Upper gastrointestinal	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lower gastrointestinal	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hepatic and pancreatic	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Renal	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Genitourinary	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Musculoskeletal and tegumental	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Neurological	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Endocrine, metabolic, breast	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychiatric	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>

Next >> clear

Figure 1. CIRS and their respective point scores. This scoring system measures the chronic medical illness ("morbidity") burden while taking into consideration the severity of chronic in 14 items representing individual body systems (Available on: <http://farmacologiaclinica.info/scales/CIRS-G/>).

Section A

Systems	Description	Scores				
Cardiac	-Any cardiac problem (angina, myocardial infarction, arrhythmia, valve problems)? -If affirmative, any medication taken for these problems? -Any heart surgery in the past?	0	1	2	3	4
Vascular	-Any circulatory problem (includes peripheral atherosclerotic disease, aneurysm of the abdominal aorta...), hypertension, or cholesterol problem? -If affirmative, any medication taken for these problems? -Any vascular surgery in the past (bypass graft surgery of lower limbs, carotid endarterectomy...)?					
Hematological	-Any blood problem (anemia, leukemia, hypercoagulability or any other problem affecting the blood, the blood cells, the spleen, or the lymphatic system)? -If affirmative, any medication taken for these problems (such as iron)? Note: Patients taking anticoagulants belong to this system if the main problem is hypercoagulability (thrombosis or recurrent embolism). If anticoagulants were taken for arrhythmias, rate the problem in Cardiac.					
Respiratory	-Any respiratory problem (asthma, emphysema, bronchitis, pulmonary embolism)? -If affirmative, any medication taken for these problems (such as pressurized aerosols)? -Any lung surgery? -Cigarette smoking? How many packs per day? For how long? Pack years = number of packs per day x the number of years smoked (example: 1 pack per day for 20 years = 20 pack years) Smoker up to 20 pack years: Rated 1 Smoker from 21 to 40 pack years: Rated 2 Smoker over 40 pack years: Rated 3					
Ophthalmological and otorhinolaryngology	-Any problem with eyes (glaucoma, cataract, important lost of vision), ears (includes important hearing impairment), nose, throat, voice? -Any medication taken for these problems (such as eye drops)? Note: Vertigo and dizziness are included in this section, unless they are of neurological origin.					
Upper gastrointestinal	-Any problem with stomach or digestion (includes the esophagus, the stomach, and the duodenum)? -If affirmative, any medication taken for these problems? -Any surgery for the stomach or the esophagus?					
Lower gastrointestinal	-Any intestinal problem (includes intestinal hernias, constipation, anal problems, incontinence...)? -If affirmative, any medication taken for these problems? -Any surgery for the abdomen?					

Section B

Systems	Description	Scores				
Hepatic and pancreatic	-Any problem in the liver or the pancreas? -Any medication taken for these problems? -Any surgery for the liver or the pancreas? Note: Cholecystectomy is rated in this section.					
Renal	-Any problem in the kidneys (impairment in function, infection...)? -If affirmative, any medication taken for these problems? -Any surgery for the kidneys?					
Genitourinary	-Any urinary problem (lithiasis, incontinence...)? -If affirmative, any medication taken for these problems? -Any surgery for the urinary bladder, for renal lithiasis?					
Musculoskeletal and tegumental	-Any problem in the skin, the joints, the bones, the muscles (includes arthritis, osteoporosis, carpal tunnel, and any other skin or musculoskeletal problem)? -Any medication, anti-inflammatory drugs? Infiltrations? Creams prescribed by a doctor? Note: Fibromyalgia is rated in this section, but it may also be rated in Psychiatric if necessary.					
Neurological	-Any neurological problem (cerebrovascular accident, peripheral neuropathy, headaches...)? -If affirmative, any medication taken for these problems? -Any surgery for these problems?					
Endocrine, metabolic, breast	-Any problem of the thyroid gland, obesity, diabetes, or any other hormonal problem? -For obesity: Body mass index (BMI) ≥ 30 : Rated 1 BMI ≥ 30 + medication or moderate disability: Rated 2 BMI ≥ 45 : Rated 3 -Any medication? Surgery for any of these problems? -Any problem with breasts (dysplasia, cancer...)? -Surgery for these problems? -Menopause (or andropause in men)? Any hormone (the same for men in andropause)? Menopause or andropause: Without hormone therapy or symptoms: Rated 0 Symptomatic or with hormone therapy: Rated 1					
Psychiatric	-Any problem of depression, anxiety, alcohol, drug abuse, or other problems? -Any medication taken for these problems? Note: Personality problems are rated in this section, but the patient's chart should be checked.					
Total score						

Figure 2 [Section A]. CIRS and their respective point scores. [Section B]. CIRS and their respective point scores.

CIRS: Please insert the appropriate grade of illness/impairment		
Organ system	If illness/impairment present, please specify:	Score
Heart		
Blood pressure		
Vascular		
Respiratory		
Ear/nose/throat		
Upper gastrointestinal		
Lower gastrointestinal		
Liver		
Renal		
Genitourinary		
Musculoskeletal		
Endocrine/metabolic		
Neurological		
Psychiatric		
		Total Score:

CAT = category; CIRS = Cumulative Illness Rating Scale; NUM = number; SCO = score; TOT = total

CIRS-CAT_{NUM}

CIRS-CAT_{SCO}

CIRS-TOT_{SCO}

Figure 3. CIRS and their respective point scores with Italian CBA software (medical records).

with worse outcomes in several CGA tests and thus with multidimensional loss of function, with MLF still significant after adjustment for comorbidity. Against the backdrop of an aging society, these findings highlight the relevance of identifying low Hb level in elderly patients at risk for adverse outcomes during nursing home stays³². This study also shows that anemia is associated with a higher total CIRS-G score, with comorbidities adversely impacting anemic prevalence and outcomes³³. The association with the CIRS-G score supports the usefulness of this score as an additional marker for frailty, whose pathogenic factors include several causes of anemia (mainly nutritional deficiencies and chronic diseases)³⁴. Protein malnutrition is usually not considered to be a cause of anemia, and its role is difficult to evaluate because malnutrition is often associated with vitamin deficiencies and comorbidities that can contribute to anemia³⁵.

However, some proteins are essential for blood cell production, so protein deficiency may indeed contribute directly to the development of anemia³⁶.

The comprehensive nature of the laboratory screen performed in all of this study's anemic patients may help to explain this difference (Malnutrition vs Comorbidity related anemia).

Complementing indicators of anemic risk, effective treatment of anemia can result in lower mortality and morbidity rates in the elderly.

However, few studies have focused specifically on anemia in the elderly or on its underlying causes. In this study, severe renal impairment was found in nearly one-third of patients and was a possible cause of anemia in almost half of the anemic patients. Although advanced age is associated with a poor response of the erythropoietic system to stress, this itself does not cause anemia³⁷. It is suggested that cytokines may inhibit erythropoiesis and thus lead to inflammatory anemia, but the precise causal mechanisms are not completely understood³⁸. It is clear, however, that renal failure must be looked for routinely as a cause of anemia in the elderly, both because renal failure is common after 80 years of age and because recombinant erythropoietin is a simple and effective, albeit underused, treatment³⁹. The implementation of CBA SIPCARplus (medical records) allows to analyze the correlation between the variables set out to increase the traceability of the information communicated and written to inter-levels. The advantages of using this software are: current data on anemic geriatric patients, evaluating the prevention of hemorrhage, assessing blood loss, monitoring and rapid laboratory assessment of coagulopathy in the setting and team work, simulation (monitoring Skill-Rule-Knowledge based errors).

The disadvantages of using this software: understanding the physiology of coagulopathy in geriatric hemorrhage and Potential Adverse Events (High-volume

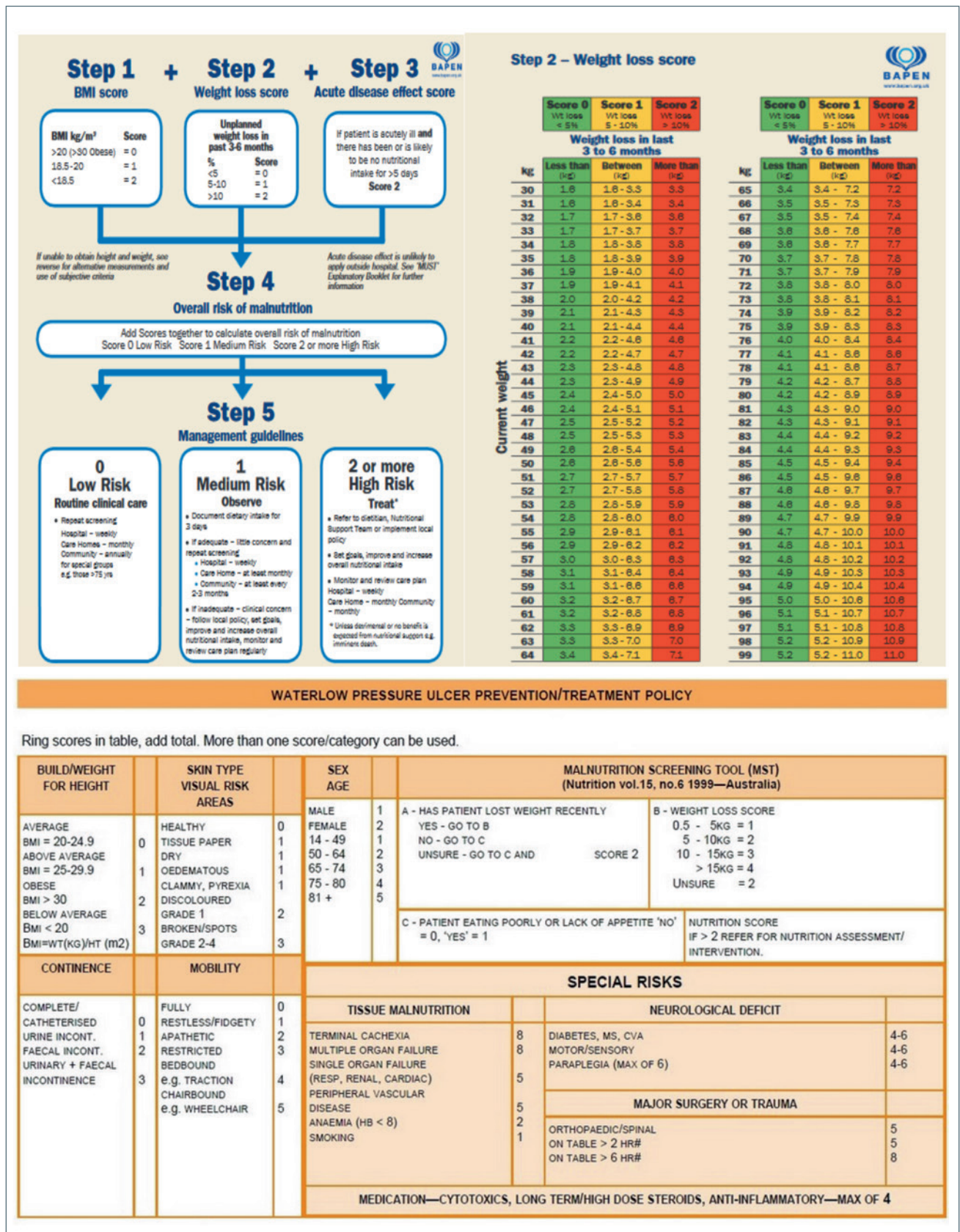


Figure 4. MUST point scores with Italian CBA software (medical records).

transfusions are associated with a risk of complications and Platelet Administration), evaluating indirect causes of anemia.

Strong aspects of this study include the training for data collectors, the overall size of the study sample, the use of an explicit conceptual framework on PBM, and the use of international, standardized tools to evaluate and describe patient characteristics.

The subgroups' sample sizes, convenience sampling and the difficulty of generalization beyond the study population represent some limitations of the research.

CONCLUSIONS

Multimorbidity is naturally prevalent in nursing home settings, particularly for those patients in whom severe renal and cardiovascular diseases are present. Therefore, the high burden of comorbidities must be taken into account when considering the high anemia prevalence in this study population.

Nevertheless, this study's results could be applied to better understand the role of PBM with CBA and biomarkers recorded in geriatric practice, transfusion thresholds, and target hemoglobin levels after transfusion. The identification of risk factors and screening markers could help notice the risk for adverse outcomes of frail elderly⁴⁰.

With regard to functionality, in this study, Hb concentration and anemia prevalence were all significantly associated with CGA test outcomes. It is possible that the association between anemia and MLF result from a direct independent deteriorating effect of anemia. With regard to cognitive function, previous studies have found anemia to be associated with cognitive impairment in specific domains as well as related to dementia and delirium⁴¹. In this study only MMSE results were significantly related to anemia, whereas group differences in CDT scores were not related.

There are many possible mechanisms by which anemia can contribute to cognitive impairment.

One, a synergistic direct vascular effect on cardiovascular diseases. Two, neuroprotection due to Erythropoietin (EPO) deficiency in the elderly. Three, an indirect effect on cognitive function which influences physical fitness and cardiac function⁴².

Questions regarding the influence of low Hb levels on distinct cognitive domains exceed the objectives of this study and should be addressed by future research. Future interventional studies could be conducted to evaluate the clinical relevance of specific geriatric criteria in transfusion indications that seem related to comorbidities. Studies are also needed to define optimal hemoglobin levels and to confirm the causal link

between anemia and laboratory test abnormalities⁴³. Finally, further studies could evaluate therapeutic interventions for anemia in the elderly, including cost effective therapeutic services aligning with multidisciplinary recommendations for pharmacy benefit management in nursing homes.

A parallel, significant restriction of healthcare costs is also predicted. Indeed, the great interest currently shown in PBM, not only in North America, has firm financial roots. According to a recent report from a Chicago-based healthcare analysis company, the "Huron Healthcare Consulting Group", PBM is one of the ten "overlooked opportunities" that could enable healthcare systems to improve the quality of their performance. PBM could reduce the cost of blood use by 10-20%, precisely through better management of this resource⁴⁴.

In this context, the multidisciplinary recommendations for the implementation of PBM in Nursing Homes are a useful instrument for healthcare staff and management in public and private structures, supporting the provision of cost-effective therapeutic services⁴⁵.

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The basophil activation test in the diagnosis and management of adverse drug reactions in the elderly

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Background and aims. The use of multi-therapeutic regimes in the elderly predisposes to frequent adverse drug reactions. The objective of the present study was to evaluate the predictive value of the basophil activation test to prevent the risk of hypersensitivity reactions in the case of potentially dangerous drugs in the elderly.

Method. This study has been conducted in the Immuno-Allergy Unit of the Policlinico Hospital, in Bari. Patients over 65 years with hypersensitivity reactions were considered. The basophil activation Flow Cast test, performed following the manufacturer's instructions, measured the degranulation of basophils, using the anti-CD63 and anti-CD203c monoclonal antibodies.

Results. 61 patients, suffering from urticaria-angioedema or anaphylaxis due to Beta-Lactam (BL) antibiotics (Group A: 28 females and 9 men; mean age 71.3) and non-steroidal anti-inflammatory drugs, NSAIDs (Group B: 20 females and 4 men; mean age 73.2), were included, as well as 2 control groups. Group C consisted of 17 women and 4 men tolerating BL and NSAIDs. Group D comprised 51 female and 19 male younger (mean age 39.7) patients with proven BL and/or NSAIDs hypersensitivity. Sensitivity and specificity were respectively 64.9% and 90.5% in group A with positive and negative predictive values equal to 92.3% and 59.4%, respectively. In the group B the respective figures were 54%, 80.9%, 6.5% and 60.7%.

Conclusions. Even though more evidences are needed to assess the suitability of the basophil activation test technique for the diagnosis of allergic reactions, this test gives promising results in the field of hypersensitivity to drugs in the elderly.

Key words: Adverse drug reactions, Basophil activation test, Elderly

INTRODUCTION

The aging population around the world is often characterized by an increased number of multiple diseases (diabetes mellitus, cardiovascular diseases, hypertension) and the necessity of a polytherapeutic regime¹. The comorbidities and correlated polytherapeutic regime cause an increased incidence of adverse drug

reactions including hypersensitivity and allergic drug reactions (ADRs). It is important therefore that a careful management of therapeutics should be put in place, by means of educational campaigns for patients and guidelines for doctors². Our previous observation confirms the possibility of ADRs in the elderly, even if the guidelines to manage these manifestations are missing in this population^{3,4}.

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The elderly patient often needs to take some drugs, responsible for a previous adverse reaction and for which there are no valid laboratory tests ⁵. Another relevant factor is the alteration in the pharmacokinetics (absorption, distribution, metabolism, excretion) and pharmacodynamics as well as the changes in the body mass in terms of total body fat and water ⁶. In addition, submitting geriatric patients to allergy tests may pose a higher risk for their health (especially in older patients with type 2 diabetes mellitus or if they take drugs such as β -blockers and ACE inhibitors, responsible for particularly severe hypersensitivity reactions) ⁷.

The present study suggests that the basophil activation test (BAT) can help the clinician in his diagnostic and therapeutic decisions (check drug responsibility and mechanism of the reaction, choose an alternative drug) ⁸. Our aim was to evaluate the BAT in terms of sensitivity and specificity and in the light of its possible clinical use in the diagnosis of allergic or pseudo allergic reactions to non-steroidal anti-inflammatory drugs (NSAIDs) and β -lactam (BL) antibiotics ⁹.

MATERIALS AND METHODS

PATIENTS

In the present study were retrospectively included patients who suffered from ADRs to either BL (group A) or NSAIDs (group B) and visiting in the Immunoallergology Unit of Policlinico Hospital, University of Bari. The BAT was conducted on geriatric subjects and compared with younger patients seen at the same unit.

For each patient has been drawn up the clinical history, the familial history, drugs taken, laboratory data and, when indicated, skin tests according to EAACI criteria ¹⁰.

Depending on the drug involved, in vitro tests were performed, including BAT (Buhlmann Lab., Basel, Switzerland), specific IgE (CAP system, Thermo Fisher Diagnostic Uppsala Sweden), determination of complement factors and circulating immune complexes, histaminemia and tryptasemia (CAP FEIA Thermo Fisher Diagnostic Uppsala Sweden).

A comparison was made between populations of young patients and geriatric patients in order to assess differences in ADR risk factors, chronic medications, pre-existing pathologies and responsible drugs. The observed patients were divided into two groups, patients under the age of 65, and patients over 65 years of age. Each group was further divided into: male and female; number of medications taken (Tab. I); verified and reported pathologies (Tab. II); drug that has probably or certainly caused ADR (Tab. III); clinical picture with which ADR is manifested (Tab. III).

Patients were selected following a careful anamnestic evaluation and with the following inclusion criteria: a reaction that occurred within 2 hours after taking the drug and occurred only when the active substance was intake; allergic reactions occurred from 1 month to 2 years before the test was performed.

All patients had suspended the use of any systemic anti-allergic drugs, such as corticosteroids, cromoglycate and H1 antihistamines at least 24 to 48 hours before blood sampling.

Non allergic exposed subjects were added as controls.

FLOW CYTOMETRY BAT

Flow Cast Kit, which uses CD63 as a basophil activation marker, has been employed. It uses a stimulating buffer containing IL-3 in the cell isolation and incubation phases of the allergen. The tests were performed according to the method described by Saint-Laudy et al. ¹¹.

Tested allergens were: penicillin V, penicillin G, amoxicillin, ampicillin, penicillin G major (PPL) and minor (MDM) determinants, cefuroxime with regard to BL antibiotics; ibuprofen, metamizole, aspirin and acetaminophen for NSAIDs. For each patient a negative control, incubating the cells only with IL-3 stimulation buffer and a positive one, incubating cells with an anti IgE (from Sigma Aldrich, Poole, United Kingdom), were performed. BATs for a drug were considered positive when triggered an activation of more than 5% of basophils and at least double the negative control. Specific IgE for ampicillin, amoxicillin, penicillin G and penicillin V has been determined (CAP-FEIA Thermo Fisher Diagnostic, Uppsala, Sweden).

Table I. Chronic therapy: differences between patients aged 65 years or over and younger patients.

Numbers of drugs	Females below the age of 65 years	Males below the age of 65 years	Females aged 65 years or over	Males aged 65 years or over
0	26	19	13	4
(1-3)	14	4	43	5
(4-6)	1	1	28	13
(7-9)	0	0	12	2
≥ 10	0	0	5	1

Table II. Pathologies verified and reported: differences between patients aged 65 years or over and younger patients.

Pathologies verified and reported	Females below the age of 65 years	Males below the age of 65 years	Females aged 65 years or over	Males aged 65 years or over
Rheumatic diseases	3	1	0	1
Allergic diseases	9	7	4	1
Autoimmune diseases	2	1	1	0
Cardiovascular diseases	13	2	30	9
Hepatic diseases	0	1	2	1
Kidney diseases	0	0	2	0
Dyslipidemia	15	5	19	7
Thyroid diseases	6	0	3	0
Diabetes mellitus	4	2	3	3
Osteoporosis	1	0	11	0
Neuropsychiatric disorders	1	1	3	1
Respiratory diseases	1	2	0	2
Hyperuricemia	0	0	1	1

Table III. Drugs responsible for adverse reactions: differences between patients aged 65 years or over and younger patients.

Drugs responsible for adverse reactions	Females below the age of 65 years	Males below the age of 65 years	Females aged 65 years or over	Males aged 65 years or over
Antibiotics	30	15	42	10
Antimycotics	0	0	1	0
Allopurinol	0	0	2	1
Antihypertensive drugs	4	4	2	0
Acetylsalicylic acid	0	0	15	9
Nonsteroidal anti-inflammatory drugs	0	0	41	9
Statins	0	0	2	1
Heparin	0	1	3	1
Contrast agents	0	0	4	1
Psychoanaleptics	9	0	4	1
Osteoporosis drugs	0	0	2	0
Oral anticoagulants	1	0	1	0
Muscle relaxants	1	0	1	0
Analgesics	5	1	4	1
Anesthetics	0	1	4	0
Antiacid drugs	1	0	6	0
Corticosteroids	0	0	5	0
Intravenous solutions	0	0	1	0
Drugs for gastrointestinal diseases	1	0	2	0
Iron therapy	0	0	1	0

ORAL TOLERANCE TEST

Subsequently, after signing an informed consent, patients underwent a tolerance test with the culprit drug in the manner and time schedules according to EAACI criteria¹⁰. All the procedures followed are in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Oral provocation tests were performed only for those drugs that triggered activations below 5%. This cut-off value was chosen on the basis of our clinical experience, considering that it never caused adverse systemic reactions, that can be particularly dangerous in elderly patients.

RESULTS

The BAT was tested in 61 geriatric patients, of whom 37 had suffered from a documented ADR that was definitely related to a BL antibiotic (group A) and 24 had suffered from ADR surely referred to a drug related to NSAIDs (group B). The clinical manifestations of ADRs were mostly urticaria-angioedema and more rarely in the form of anaphylactic shock or a cell-mediated reaction (Tab. IV). Clinical manifestations were urticaria-angioedema in 35 cases and anaphylaxis in 2 in group A, and 24 had suffered from urticaria-angioedema in group B. As a control population, a group of 21 geriatric patients was selected, of whom 13 with allergies to inhalants, who had never had any allergic reactions to drugs and had taken NSAIDs and BL antibiotics in the last year (Group C). Group A consisted of 28 women and 9 men, averaging 71.3 years (range 68-82); 4 among them were also affected by allergy to inhalants and foods. Group B consisted of 20 women

Table IV. ADR clinical manifestations: differences between patients aged 65 years or over and younger patients.

ADR clinical manifestations	Females below the age of 65 years	Males below the age of 65 years	Females aged 65 years or over	Males aged 65 years or over
MPE	2	1	0	0
Urticaria angioedema syndrome	40	21	93	25
Anaphylaxis	1	0	8	1

ADR: allergic drug reaction; MPE: maculo-papular eruption

and 4 men, averaging 73.2 years (range 66-85); 1 was also affected by food allergy. Group C consisted of 17 women and 4 men, averaging 70.9 years of age (range 66-75). In 14 patients of group A and 5 of group B, who had reintroduced the active substance, the reaction was reproduced. We also considered a control group made of younger patients (Group D, 51 female patients, 19 male patients, average age 39.7).

Medications mostly used for a chronic disease were antibiotics, NSAIDs, antihypertensive, diuretics, insulin, oral hypoglycemic drugs, statins, psychoanaleptics, heparin. As age advances, more diseases develop and more medications were needed. Most of the medicines taken were for the treatment of cardiovascular diseases, diabetes and dyslipidemia.

Finally, with regard to the presence of other allergies (inhalants, foods etc.), only 20.6% of geriatric patients (groups A and B) exhibited an allergy-confirmed disease compared to 58.4% of non-geriatric patients (Group D). With particular reference to Flow Cast, in group A 24 out of the 37 patients were positive with at least one of the culprit tested drugs (sensitivity = 64.9%). 10 patients were positive to PPL, 5 to MDD, 11 to amoxicillin, 8 to ampicillin, 10 to penicillin G, 12 to penicillin V and 4 to cefuroxime. Only in 7 cases the result was positive for one drug only: 2 PPL, 3 MDM, 1 amoxicillin and 1 penicillin G. In group C, 2 patients had activations above the established cut-off with drugs that they tolerated: 1 to ampicillin and 1 to amoxicillin (specificity = 90.5%). Specific IgEs were positive to at least one

of the drugs tested in 9 cases (sensitivity = 24.3%). In group B, 13 patients out of 24 had significant activation of basophils with the drug responsible for the reaction (sensitivity = 54%). 10 patients were positive to aspirin, 6 to ibuprofen, 5 to metamizole, 9 to acetaminophen. In 9 cases activation was induced by one other drug not involved in the index reaction: 4 by aspirin, 2 by ibuprofen, 3 by metamizole. In group C, 4 patients had higher activation than the cut-off for aspirin (2 cases), metamizole (1 case), ibuprofen (1 case) (specificity = 80.9%). Positive predictive value was 92.3% for BL antibiotics and 76.5% for NSAIDs, while negative predictive value was 59.4% for BL antibiotics and 60.7% for NSAIDs (Tab. V).

In both groups of patients, the response was not influenced by the time elapsed since the allergic reaction, as positive responses were also found in cases of reactions dating back to 2 years earlier. The in vivo provocation tests performed, following Flow Cast and according to the above-mentioned selection criteria were negative in 5 patients with allergy to BL antibiotics (and challenged with another BL) and 4 with hypersensitivity to NSAIDs and challenges with another NSAID, thus confirming the good negative predictive value.

DISCUSSION

The identification of the antigens responsible for allergic reactions is essential both for diagnostic purposes and for effective prevention measures in relation to these manifestations. Diagnostic protocols require, in most cases, an accurate collection of anamnestic data, in vivo tests and when available, laboratory tests. As regards the diagnosis of drug allergy reactions, in vivo tests are not without risk, in particular for elderly patients with chronic pathologies, especially respiratory and cardiovascular, for whom the induction of an anaphylactic shock after oral provocation tests could be dangerous and even lethal¹³. Considerably lacking is laboratory diagnostics. In fact, in the laboratory, allergen-specific IgE are detected, but only immunoassays for a few drugs are available and scientifically validated; moreover, this test is not very sensitive and tends to become negative in a short time. Some drugs,

Table V. BAT in immediate BL- antibiotics and NSAIDs hypersensitivity.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Group A (BL antibiotics)	64.9	90.5	92.3	59.4
Group B (NSAIDs)	54	80.9	76.5	60.7

particularly NSAIDs, may also induce degranulation of effector cells by means of leukotrienes, complement or by direct action of the drug and not by means of IgE¹⁴. In recent years, a lot of scientific studies have highlighted the potential use of cytofluorometry for in vitro diagnostics of allergic diseases¹⁵. It has been seen that, under pacing with a specific allergen, basophils release active mediators in quantifiable doses and regulate the expression of markers that can be easily measured by flow cytometry using specific monoclonal antibodies¹⁶. Basophils are granulocytes that develop from CD34 + pluripotent stem cells, mature in the bone marrow and then pass into the bloodstream where they represent less than 1% of the leukocytes. Basophils show a segmented nucleus and possess rounded granules containing glucosaminoglycans, heparin and histamine in their cytoplasm. These granules are called “basophilic” because they have a particular affinity for the basic dyes mainly due to the presence of heparin and hyaluronic acid. Basophils express receptors for interleukins, chemokines, complement proteins, prostaglandins and for the Fc fragment of IgE^{17 18}.

The base of the basophil activation test is a demonstration of the change in the membrane phenotype of basophils that after allergenic stimulation can have an up or a down regulation¹⁵. The basophil activation test, which can be performed with any suspected drugs, measures the activation of basophils after stimulation and is suitable for both IgE-mediated and non-IgE-mediated hypersensitivity. Clinical studies utilizing flow cytometry for measurement of markers of basophils activation have primarily focused on 2 markers, CD63 and CD203c: CD203c, expressed exclusively on basophils and mast cells and their progenitor cells, is, as CD63, overexpressed during activation of these cell types¹⁷.

CD63 (gp 53), present in different cells (basophils, platelets, monocytes, mast cells). It is contained in intracytoplasmic granules and when in activation it is expressed in high density on the cell surface¹⁸.

The basophilic activation study technique makes use of a flow cytofluorometry method based on the use of fluorochromes with monoclonal antibodies, which specifically identifies surface markers expressed on the membrane of the cells, in this case basophils CD63 and CD203c. Subjects with a degranulation percentage of 5% or more should be considered susceptible to allergy or have a positive stimulation. The results we have obtained in the case of BL antibiotics reveal a higher BAT sensitivity compared to the results reported in the literature and a slightly lower specificity¹⁹. In the case of NSAIDs, however, the sensitivity found is greater than the results reported in the literature, with a lower specificity²⁰. However, although the sensitivity found is not high, the negative predictive value is of interest since

we have not found any adverse events to drug administration in the negative test patients, according to the criteria previously reported. However, an extended prospective study would be needed to confirm these results. BAT can be used to reduce pretest probability of having unwanted reactions to the provocation test, which remains the gold standard for diagnosing of drug allergy. Moreover, BAT is also useful for the diagnosis of those hypersensitivity reactions that do not recognize an IgE-mediated mechanism, as in the case of NSAIDs. As it is a relatively recent method, it has not been fully standardized yet. Some questions concern the optimal drug concentration to be used for the test (too low concentrations can give false negatives, as well as too high concentrations can give false positives, due to the possible cytotoxic effect); in addition, the sample of blood must be analyzed no later than 24 hours after collecting and on a minimum number of basophils. The use of BAT is however an advantage from a clinical point of view, especially when referring to a category of patients, such as the geriatric one, where it is imperative to recognize accurately any hypersensitivity to drugs in the elderly, often affected by multiple diseases^{21 22}. The same would hold true for infants and for severe reactions in which a drug provocation is not permitted.

ADRs represent a major impact on society, resulting in significant morbidity, mortality, and health care costs. They can mimic the clinical picture of other illnesses, causing unnecessary investigations, or preclude the use of certain drugs by the doctor, and so postponing the therapeutic treatment. The budget can be addressed to the right direction if it joins simple guidelines²³ such as: 1) collect a careful pharmacological history: the disease to be treated can be iatrogenic or the drugs taken may interact with prescription; 2) prescribe only for a specific diagnosis; 3) define the purpose of the therapy and start with small doses titling on the desired response; 4) maintain a high level of suspicion of drug reactions and interactions and know what other drugs the patient is taking; 5) simplify the treatment regime as much as possible and limit the number of drugs to be taken.

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Reliability and validity of Turkish version of “Physical Fitness and Exercise Activity Levels of Older Adults” Scale

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Background and aims. This research aimed to investigate the reliability and validity of the Turkish version of the Physical Fitness and Exercise Activity Levels of Older Adults Scale.

Methods. Methodological study was conducted at an elderly care centre. The study sample comprised of 347 residents. The Physical Fitness and Exercise Activity Levels of Older Adults Scale was used for reliability and validity analysis.

Results. The overall content validity index value for overall scale was 0.91. KMO sample coefficient of concordance was found as 0.87, Barlett's test χ^2 value is calculated as 1736.3 ($p = 0.000$). Compatibility values were RMSEA = 0.08, RMR = 0.05, CFI = 0.88, GFI = 0.89, AGFI = 0.86. Internal consistency reliability was 0.89, corresponding coefficients for the perceived motivators factor was 0.88, for the perceived barriers factor was 0.78 and the physical fitness factor was 0.86. In contrast to the original 41-item scale, the number of items in the scale used in the present study was reduced to 34 after the confirmatory factor analysis.

Conclusions. The study demonstrated that this scale is a valid and reliable instrument that could be used to determine exercise-related motivators and barriers perceived by individuals aged ≥ 60 years.

Key words: Older adults, Reliability, Exercise, Factor analysis

INTRODUCTION

Regularly performed physical activities and exercises are known to improve not only the psychosocial, but also the physical and emotional health of older adults, and to offer several benefits¹. If performed daily, even a very low level of physical activity has been reported to play an important role in reducing the risk of coronary heart disease². In addition to the aforementioned benefits, regular exercise contributes to the maintenance and improvement of functional health, reduce the risk or delays the development of diseases such as diabetes mellitus and osteoporosis, promotes immune functions, regulates sleep patterns, reduce colorectal cancer risk,

regulates blood pressure, improves cognitive capacity, facilitates weight control, reduces anxiety and can effectively treatment mild depression in older adults³. All evidence obtained from comparisons of physically active and inactive people aged ≥ 65 years suggests that the former group has lower mortality rates related to coronary heart disease, high blood pressure, stroke, type 2 diabetes mellitus, lower colon cancer and breast cancer; improved heart, lung and muscle health; a healthier body mass and composition and an improved biomarker profile; all of these factors reduce the risk of the development of cardiovascular diseases and type 2 diabetes and ensure better bone health in the former group⁴. Physical exercise reduces the risk of disease

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through assist with weight control and prevention of obesity in populations. Thirty minutes of activity per day would, on average, be expected to confer additional protection against the development of diabetes and cardiovascular disease and would assist with weight control and prevention of obesity in populations with low baseline activity⁵. Despite the known benefits of physical activity and exercise, however, most older adults are not physically active, and the number of people in this age group who participate in regular exercise is very low⁶. In 2009, physical inactivity was identified as the fourth leading risk factor for non-communicable diseases and accounted for more than 3 million preventable deaths⁷. Physical inactivity was responsible for 13.4 million DALYs worldwide⁸. Inactivity increases with age in all World Health Organization (WHO) regions, which is a pattern known to have a strong biological basis. The frequency of inactivity in older adults varied between WHO regions: 30% of older adults are inactive in south-east Asia, 40% in Africa, 47% in western Pacific, 49% in Europe, 55% in the eastern Mediterranean, and 62% in the Americas⁷.

In recent years, among older populations, the concept of healthy ageing has developed. Physical activity is associated with better physical health and is a priority of public health with a successfully ageing population⁹. According to the health belief and health promotion model, the perceived barriers obstruct the behavior while the perceived motivators facilitate the behavior. A positive perception towards physical activity may encourage older adults to develop it¹⁰. Despite considerable emphasis on the importance of physical activity to the realization of healthy lifestyle behaviours among the older adults, little information is available regarding the motivations of older adults to be physically active or the factors preventing physical activity in this population. Motivators for activity include enhanced physical and psychological health and independence, chronic condition management, social interaction and support, advice from medical professionals, and enjoyment in the elders¹¹⁻¹³. Clearly, more research is needed to determine the nature (consistency and perception) of physical activity barriers and motivators among older adults. Studies on this issue have demonstrated that performing group exercise activities and the presence of family support and community resources are perceived by the elderly as exercise motivators^{6,14}. Deci & Ryan classified these motivators as intrinsic and extrinsic. High levels of intrinsic motivation are connected to feelings of enjoyment and low levels of anxiety. An extrinsically motivated, on the other hand, engages in an activity for its subsequent positive outcomes, such as exercising to improve health or to lose weight¹¹. In older adults particularly, the barriers that permeate their

engagement in physical activity involve the following: fear of falling or injury, fear of being victim of violence when exercising outdoors, fatigue, morbidity, physical limitation, pain and also lack of companionship, lack of time and lack of family encouragement¹⁰. Sechrist et al. reported that the most important factors that affect the performance of physical activities are healthy lifestyle behaviors, perceived benefits, perceived barriers, health problems, low perceptions of self-efficacy and health, advanced age, income inequality and shortage of time¹⁵. According to Olanrewaju et al. barriers include health status, previous physical activity habits and experiences, and cultural sensitivity, while facilitators include enjoyable activities and convenient scheduling¹⁶. Common categories of barriers that have been identified include environmental (e.g., access to facilities or transportation, safe walking routes, lack of social support from significant others such as verbal persuasion from medical professionals and others not to exercise, weather), and personal (e.g., facility cost, dislike of exercise, depression, fear of injury, lack of time and/or motivation, perceptions of age appropriateness and capabilities, physical ailments such health, joint pain, and injury).

Within the scope of advanced nursing practices, nurses are expected to perform comprehensive health diagnostics and recommend lifestyle changes related to the health conditions of older adults, with the intent to identify exercise-related benefits and barriers perceived by the older adults. Therefore, advanced nursing practices should include data collection, which ensures that the older adults become aware of factors preventing them from exercising and determines their perceptions of health status. Ensuring the participation of older adults in healthcare plans, including self-care-related aims such as physical fitness and exercise, is a standard of gerontological nursing practices¹⁷.

For older adults, physical activity measurement is complicated because they often engage in lighter activities more frequently than in moderate or vigorous activities and they may perform activities on an irregular basis, making it difficult to recall. There are widely used international scales to assess the type, frequency, weekly duration-hours and intensity (kcal/min-1) of physical activity in the elderly^{13,18-20}. Because these scales assess physical activities performed only within the past week, they cannot be used to determine perceived barriers and motivators regarding exercise. The Community Healthy Activities Model Program for Seniors (CHAMPS) Questionnaire, the Physical Activity Scale for the Elderly (PASE), and the Yale Physical Activity Survey (YPAS) were developed for community-dwelling older adults^{13,18-20}. These three surveys ask about the duration of activity performed over one week rather than per

session to facilitate recording of irregular activity. The YPAS allows the estimation of PA of a typical week in the last month prior to evaluation (PA type, duration-h. wk and intensity-kcal.min-1) in five domains (household, yard work, caregiving, exercise, and recreational activities) ¹⁸. The CHAMPS survey was developed to assess outcomes of a physical activity promotion intervention designed to change activity behavior. The questionnaire assesses weekly frequency and duration of various physical activities (light, moderate, and vigorous physical activities) typically undertaken by older adults in the last four weeks ¹⁹. The Physical Activity Scale for the Elderly was developed by Washburn et al. in 1993 to assess older adults' performance of physical activities at home, work, or for recreation ¹³. This scale assesses participants' walking, light/moderate/strenuous sporting and recreational activities within the last week, muscular strength and endurance exercises, work-related activities such as walking and standing, lawn work or yard care, providing care for someone else, home repairs and light or heavy housework requiring physical activity ¹². The Physical Fitness and Exercise Activity Levels of Older Adults Scale (PFES) is a tool based on a health promotion model used to determine factors motivating an elderly person to exercise or preventing him/her from exercising. There is any scale to assess the physical fitness and exercise activity levels of older adults in Turkey, and we used PFES since that its' items are short and designed considering the level of literacy of older adults and easy to understand by the elderly people. In addition, the scale measures the frequency of physical activity in general, without a time limit such as last week, last four weeks. The purpose of this research is to test the reliability and validity of Turkish version of the "Physical Fitness and Exercise Activity Levels of Older Adults" Scale. It is expected that this tool could be used to determine factors motivating elderly people to exercise or preventing them from exercising in clinical settings, nursing homes, as well as in research. Within the scope of the study, the following research problems were sought:

- Do the items of the Turkish form yield the same meanings as the items in the original form?
- Is the reliability of the scale items sufficiently high?
- Is the scale acceptably stable over time?
- Is the factor structure of the Turkish scale similar to that of the original form?

MATERIAL AND METHODS

RESEARCH TYPE

This is a methodological study to evaluate the validity

and reliability of the 'Physical Fitness and Exercise Scale for the Older Adults'.

SAMPLE

The study was conducted between March 15, 2014 and December 20, 2014 at an elderly care centre affiliated with the Provincial Directorate of Izmir of the Ministry of Family and Social Policies. This elderly care centre houses retirees older than 60 years who receive pensions from the Turkish state retirement fund. The centre residents also receive medical and social services. Primary health care services are provided to these residents by family physicians, nurses and healthcare providers who work in primary healthcare services.

Inclusion and exclusion criteria: Individuals who aged 60 years or older, lived in the elderly care center, had no hearing problems, could independently perform activities of daily living, and agreed to participate in the study were included in the sample. Those who had a neurologic condition (dementia, Parkinson or stroke) and those who did not meet any of the inclusion criteria were excluded from the study.

The population of this methodological study comprised 792 elderly residents of the aforementioned elderly care centre. Of these residents, 30 did not want to participate in the study and 415 were on a summer holiday. Therefore, the study sample comprised the 347 residents who remained at the elderly care centre had no hearing problems and agreed to participate in the study. According to the literature, the recommended size of a methodological study sample is five- to 10-fold the number of items in the scale ²¹. Therefore, the size of the sample in this study was considered of sufficient in number.

DATA COLLECTION TOOLS

The following tools were used to collect data:

1. Sociodemographic characteristics questionnaire: this questionnaire comprises eight questions regarding the sociodemographic characteristics of the elderly;
2. Physical Fitness and Exercise Activity Levels of Older Adults Scale (PFES): This scale was developed by Melillo et al. in 1997 to assess the physical fitness level of older adults as well as their perceived motivators and barriers and exercise frequency ²². The scale has 41 items within four subscales: physical fitness, perceived barriers, perceived motivators and exercise frequency. The minimum and maximum possible scores of the overall scale are 41 and 164, respectively. Possible subscale and item scores are as follows:
 - physical fitness subscale: this subscale comprises nine items, with minimum and maximum possible

scores of 9 and 36, respectively. A higher score indicates a lower physical fitness level;

- perceived barriers subscale: this subscale comprises 13 items, with minimum and maximum possible scores of 13 and 52, respectively. A higher score indicates a higher number of perceived barriers;
- perceived motivators subscale: this subscale comprises 11 items, with minimum and maximum possible scores of 11 and 44, respectively. A higher score indicates a lower number of perceived motivators;
- exercise frequency subscale: this subscale comprises eight items, with minimum and maximum possible scores of 8 and 28, respectively.

Items in the physical fitness, perceived barriers and perceived motivators subscales are rated using a four-point Likert scale (1 = Strongly Agree, 2 = Agree, 3 = Disagree, 4 = Strongly Disagree). Items in the exercise frequency subscale, which indicate how frequently the subject participates in physical activities, are also rated on a four-point Likert scale (1 = Never, 2 = Once a week, 3 = 2-3 times a week, 4 = Daily).

TRANSLATION PROCESS AND CONTENT VALIDITY

The scale was translated into Turkish by three experts and back-translated into English by two additional experts. The opinions of eight experts regarding content validity were obtained. Davis expert technique was applied to evaluate the content validity of the scale items²³. Specifically, the experts were requested to evaluate the items as (a) 'is appropriate', (b) 'needs minor revision', (c) 'needs major revision', or (d) 'is not appropriate'. According to this technique, the number of the experts who marked the (a) and (b) options was divided by the total number of the experts to obtain a 'content validity index' was obtained.

DATA COLLECTION

Data were collected through face-to-face interviews conducted in the lounge of the elderly care centre. Because of decline in the elderly participants' perception and hearing abilities, each interview required approximately 20-25 min. The scale was re-administered to 36 elderly people in the sample who were re-contacted as a post-test for reliability after a 2-week interval. Participants were asked to write not any personally identifiable information other than a nickname on the questionnaire during both the first and second administration of the scale and the test-retest applications.

DATA ANALYSIS

Data were analysed using SPSS 22 (Statistical Package for the Social Sciences) software (SPSS, Inc., Chicago,

IL, USA). SPSS AMOS version 22 was used for the confirmatory factor analysis (CFA). Mean, minimum and maximum values were used for numerical data, whereas numbers and percentage calculations were used for categorical data. Regarding the reliability analysis, item-total correlations were used to determine item reliability, and Cronbach's alpha was used to determine homogeneity. The test-retest and Pearson product moment correlation methods were used to evaluate the stability of the scale over time. A value of 0.30 was used as a criterion for item-total correlations^{24 25}. Exploratory factor and confirmatory factor analyses were used to determine the construct validity of the scale. Determining the suitability of the data for factor analysis, Kaiser-Meyer-Olkin (KMO) and Bartlett's tests were implemented^{26 27}.

A basic component factor analysis was performed to distinguish the subscales from each other while assessing construct validity. Factor loadings were determined using the Varimax method. Hotelling's T² test was used to investigate whether the scale items were perceived similarly by the elderly, whether understanding difficulty levels were similar and whether they were distributed normally²⁸. A p-value of < 0.05 was used to indicate significance.

ETHICAL ISSUES

Written permission to translate the PFES into Turkish and use it was obtained from Melillo K by e-mail (personal communication). Written approval and Permission to conduct this study was received from the institutional non-interventional ethical committee and from the Provincial Directorate of Izmir of the Ministry of Family and Social Polices. An informed consent form including information about the purpose of the study, the length of time it would take to complete and participants' rights was signed by the participants. Participants were assured that the questionnaire was anonymous, participation was voluntary and they could withdraw from the research at any time and the data collected would be kept confidential.

RESULTS

The mean age of the individuals participating in the study was 77 ± 7.9 years (min-max: 60-94 years). In addition, 64.8% were female, 66.6% were high school/college graduates and 47.0% were widows or widowers.

CONSTRUCT VALIDITY OF TURKISH PFES

Content validity

Back-translation method was used to translate to Turkish version. The scale was translated into Turkish

by three experts and back-translated into English by two additional experts. The final Turkish version was reviewed by eight faculty members (expert panel) to assess the suitability and clarity of its language, intelligibility, and understandability. Specifically, the experts were requested to evaluate the items as (a) 'is appropriate', (b) 'needs minor revision', (c) 'needs major revision', or (d) 'is not appropriate'. According to this technique, the number of the experts who marked the (a) and (b) options was divided by the total number of the experts to obtain a 'content validity index' was obtained. The overall content validity index value for all scale items of the scale was 0.91. To determine the clarity of the items in the scale, the scale was pilot-tested among 10 elderly people with characteristics similar to those of the participants but who had not been included in the sample. The pilot testing demonstrated that the items were sufficiently clear and understood by the participants. Minor changes in wording were made and final form showed no linguistic problems and finally content and face validity of the Turkish version of the scale were satisfactory.

Construct validity

To establish the construct validity of the scale, a factor analysis was conducted. The KMO value of the scale was 0.87. The significance of the Bartlett's test was $p = 0.000$ ($X^2 = 1736.3$). A confirmatory factor analysis of the construct validity of the scale yielded the following compatibility values: RMSEA = 0.076, RMR = 0.06, CFI = 0.77, GFI = 0.78, NFI = 0.70, AGF = 0.75 ($p < 0.05$). In the confirmatory factor analysis, items with values of < 0.70 or near 0.070 were revised; a repeated confirmatory factor analysis yielded the following values: RMSEA = 0.08, RMR = 0.05, CFI = 0.88, GFI = 0.89, AGFI = 0.86 ($p < 0.05$; Tab. I).

The factor structure of the scale was subjected to an exploratory factor analysis, in which three factors were determined to have eigenvalues > 1 . The eigenvalues were 9.57 for the first factor, 3.56 for the second factor and 2.26 for the third factor, and

these factors accounted for 38.38%, 13.74% and 8.69% of the variance, respectively. Therefore, the three-factor structure accounted for 60.83% of the variance. Table II shows the loads and eigenvalues of the scale items. Load factors ranged from 0.320 to 0.903 (Tab. II).

RELIABILITY OF THE SCALE

Internal consistency analysis and mean scores of the Turkish PFES

The total mean score for the overall scale was 80.0 ± 10.1 (Tab. III). The mean scores obtained from the subscales were as follows: 18.2 ± 4.6 for the motivators subscale, 32.03 ± 6.1 for the barriers subscale, 16.3 ± 3.8 for the physical fitness subscale and 13.4 ± 3.9 for the exercise frequency subscale. The lowest and highest mean scores were obtained for item 31 (1.96 ± 0.69) and item 12 (2.88 ± 0.84), respectively (Tab. II). The distributions of the mean item and overall scale scores are presented in Table II.

In contrast to the original 41-item scale, the number of items in the scale used in the present study was reduced to 34 after the confirmatory factor analysis; the four-factor internal consistency coefficient used to test internal consistency reliability was 0.89. The corresponding coefficients were 0.88 for the perceived motivators factor, 0.78 for the perceived barriers factor and 0.86 for the physical fitness factor (Tab. III). A Cronbach's alpha of 0.76 was calculated after obtaining data from 36 subjects who were contacted a second time to determine the test-retest reliability of the scale. In addition, item-total correlations and Cronbach's alpha coefficients for each scale item were calculated using the item-elimination method. Cronbach's alpha coefficients ranged from 0.88 to 0.89. The scale item and reliability analyses yielded item-total correlations of 0.215-0.737, which were considered significant ($p = 0.001$). The analysis of the relationship between each subscale's score and the overall scale score demonstrated that the reliability coefficients ranged between 0.60 and 0.81 ($p = 0.000$).

Table I. Compatibility values of the scale.

Compatibility values	CFA Analysis-I	CFA Analysis-II
Chi-square/ p-value	1736.3/p = 0.000	840.340/291
CMIN/df	2.98	2.88
Degrees of freedom	581	291
RMSEA	0.076/p < 0.05	0.08
RMR	0.06	0.05
CFI (Comparative Fit Index)	0.77	0.88
GFI (Goodness of Fit Index)	0.78	0.89
AGFI (Adjusted Goodness of Fit Index)	0.75	0.86

Table II. Subscales and distributions of factor loading, item-total mean scores and correlation coefficients.

Factors	Factor loading	Mean	SD	Item-total correlations	Variance
Physical fitness					
9. I am physically fit.	,774	2,00	,66	,488	%8.69
10. I can do more than most people my age.	,844	1,91	,69	,475	
17. I have a lot of energy.	,607	2,55	,77	,536	
18. I feel able to face the day when I get up in the morning.	,793	1,98	,57	,471	
19. I feel physically able to do what I want.	,756	2,10	,67	,580	
21. I feel that my mind and body work together.	,522	1,82	,63	,405	
28. I can take care of myself.	,490	1,81	,59	,526	
29. I can do a lot more for my age.	,484	2,13	,74	,428	
Barriers					
12. I am concerned that I will hurt or strain myself if I am too physically active.	,676	2,88	,84	,361	%13.74
13. I sometimes get tightness in my chest when I exert myself.	,320	2,27	,89	,401	
14. I have too little time for exercise.	,578	1,99	,77	,295	
16. I do not have the strength to exercise.	,505	2,23	,81	,647	
24. I am not interested in exercise.	,476	2,34	,83	,441	
34. It is difficult to exercise if I feel depressed.	,476	2,81	,84	,249	
35. Lack of transportation limits my exercise options.	,782	2,16	,85	,270	
37. Bad weather prevents me from exercising.	,728	2,27	,87	,215	
39. I sometimes get short of breath when I exercise.	,770	2,26	,85	,411	
40. Fear of falling prevents me from exercising.	,688	2,60	0,88	0,41	
Motivators					
15. I prefer to be in a scheduled exercise program.	,735	2,49	0,92	,27	%38.38
22. I feel better when I am active.	,439	1,68	,54	,446	
25. Exercising gives me more energy.	,793	2,13	,76	,737	
26. Exercising gives me a sense of accomplishment.	,890	2,09	,73	,651	
27. Exercise keeps my mind active.	,844	2,02	,72	,629	
30. Exercise is good for my heart.	,857	2,00	,68	,676	
31. Exercise helps my spirits.	,903	1,96	,69	,695	
32. I exercise to keep myself healthy.	,710	2,23	,77	,581	
Total					60.83

Test-retest variability

The internal consistency and test-retest stability of the scale was estimated as the bivariate correlation between the baseline and follow-up PFES scores by administering the same test twice over a period of two weeks to 36 elderly participants selected from the study group. The test-retest correlation value was determined to have a Pearson r value of 0.76 ($p = 0.000$). The analysis determined that the mean values were different with a Hotelling's T^2 value of 28.75 ($p = 0.0000$), indicating that the participants responded to the items differently and that the responses were reliable.

Internal consistency analysis

Three of the four subscales were subjected to validity and reliability analyses. Of the 34 items of the three subscales, seven items (11, 20, 23, 33, 36, 38, 41) were removed (range: 0.20-0.50). The item-total correlation

values of the same items were either < 0.30 or negative. Of the remaining 26 items, 20 (items 9, 10, 13, 16-19, 21, 22, 24-32, 39, 40) had correlation values > 0.40 (Tab. II) and were therefore considered very distinctive. Five items (items 14, 15, 34, 35, 37) had correlation values between 0.20 and 0.30 and needed revision. Because the confirmatory factor analysis values of these five items were > 0.70 , they were not removed from the scale.

DISCUSSION

It is important to determine what factors motivate older people to involve in more physical activity or prevent them from doing so. It is also important to use a standard measuring instrument to determine these factors. This present study is the first one in which the PFES

was used in a language other than the original language to assess the physical fitness level of older adults as well as their perceived motivators and barriers and exercise frequency.

For psychometric assessments of scales, the content validity index values calculated after receiving expert opinions should equal or exceed 0.80, according to the Davis method²³. In the present study, the content validity index values met this criterion. The psychometric properties of the scale were determined to be good²¹. According to the determined criteria, the KMO value of the present study was adequate²⁹. When determining the construct validity of the scale, the goodness of fit index in the CFA should meet the desired level. Based on these values, the scale compatibility was considered good (≥ 0.95 indicates perfect compatibility, 0.90-0.95 indicates good compatibility and 0.80-0.90 indicates compatibility)³⁰.

The following items were removed from the scale: item 11 "I feel well whether or not I am physically active"; item 20 "I cannot do a lot of movements I was able to do in the past"; item 23, "If my health were better, I would be more active"; item 33, "When I have pain, it becomes hard to exercise"; item 36, "I want to exercise of my own free will, not when someone else tells me to do so"; item 38, "I feel better when I am active" and item 41, "I prefer to exercise together with others". So the Turkish form of PFES was consisted of four-factor with 34 items. In the present study, the four-factor structure of the original scale was also confirmed with the confirmatory factor analysis, and four-factor model fit reasonably well, with the sample data. In addition, in the original study, factor analysis was not performed and the necessity of performing factor analysis in larger sampler was emphasized²². Therefore, the present study also gives the results of the factor analysis of the Melillo et al.'s scale.

Internal consistency analysis

Reliability is defined as the consistency or repeatability of measurements obtained from a test or measurement instrument administered to a particular population or sample^{27 29 31}. The alpha coefficient is used to test

internal consistency²⁹. A Cronbach's alpha coefficient of < 0.40 indicates that the tool is not reliable, whereas values of 0.80-1.00 indicate very good reliability²⁷⁻²⁹. Melillo et al. determined Cronbach's alpha values of 0.76 for the overall scale, 0.78 for the physical fitness subscale, 0.88 for the perceived motivators subscale and 0.72 for the perceived barriers subscale. A Cronbach's alpha value was not calculated for the exercise frequency subscale²². In the present study, the Cronbach's alpha value for four-factor structure scale is very reliable. Therefore, the reliability of in the Turkish version of the PFES are similar to or higher than those of the subscales of the original scale.

In the item-total item correlations, values of ≥ 0.40 are considered very distinctive, values between 0.30 and 0.40 are considered distinctive. Items that represent values between 0.20 and 0.30 need revision 24-26. Seven items were removed from the scale because their factor scores were significantly low (< 0.5). Of the remaining 26 items, 20 items were considered as very good distinctive items (> 0.40).

The test-retest method is implemented to determine a correlation between two measurements of a test administered to the same individuals under the same conditions at a certain time interval²⁸. The test-retest value of the original scale was 0.61. The test-retest-reliability coefficient in this study, which exceeded 0.70 (Pearson's $r = 0.76$, $p = 0.000$), demonstrated that this tool is capable of providing similar measurement values during repeated measurements. Hotelling's T^2 test was used to investigate whether the participating elderly subjects gave the same responses to the survey items²⁸. The results of Hotelling's T^2 test revealed that the mean scores of the scale items showed that the participating elderly had low levels of physical fitness, neither many nor few perceived barriers related to exercise, few perceived motivators and a lower frequency of exercise.

In the present study, the total score for the overall scale was 80.0 ± 10.1 (Tab. III). In Melillo et al.'s study, the total score for the overall scale was 100.96 ± 12.47 ²². In the present study, the total scores the elderly obtained from the PFES scale was lower, they had more barriers, fewer

Table III. Subscale reliability values.

Factors (item number)	$\chi \pm SS$	Min-Max	Cronbach alpha	Sub-total Scale correlations*
Factor 1: motivators (15, 22, 25-27, 30-32)	18.2 \pm 4.6	11-44	0.88	0.70
Factor 2: barriers (12-14, 16, 24, 34, 35, 37, 39, 40)	32.03 \pm 6.1	13-52	0.78	0.81
Factor 3: physical fitness (9, 10, 17-19, 21, 28, 29)	16.3 \pm 3.8	9-36	0.86	0.60
Factor 4: exercise frequency (1-8)	13.4 \pm 3.9	8-28	-	-
Total	80.0 \pm 10.1		0.89	

* Pearson correlation analysis, $p = 0.000$

Cronbach's alpha values were not calculated for the Exercise frequency subscale.

motivators, lower physical fitness and moderate exercise frequency. In Mellillo et al.'s study, motivators score was higher (33.2 ± 4.4), barriers score was lower (29.3 ± 4.1), physical fitness score was higher (27.9 ± 3.1) and exercise frequency was similar (14.1 ± 3.3)²².

Barriers – and motivators – related perceptions of from different cultural groups may vary. Motivators such as education, treatment of co-morbid conditions, group exercising, safety, past positive experiences are important variables to increase compliance to exercise. However, barriers such as poor health, unfavorable weather conditions, fear of falling are major obstacles to the initiation and maintenance of exercise behavior. It will be useful to identify motivators and barriers for elderly people to start exercising and to assess their compliance. This scale can be applied to different samples in different societies to determine the barriers and motivators that affect the physical activity frequency of the elderly. The data obtained will guide the planning of interventions to increase the frequency of physical activity and to improve quality of life.

LIMITATIONS

The literature recommends that the parallel forms technique be used in analyses of the reliability of a questionnaire²⁷. This study is limited by the lack of a parallel form reliability analysis; however, parallel forms were not used because of the elderly subjects' difficulties with reading and comprehension. Since that the original scale has not been adopted yet into an other language. Another limitation of this study is that we could not compare the findings with those of other cultures.

CONCLUSIONS

The Turkish version of the 34-item, 4-subscale PFES showed statistically acceptable levels of reliability and validity. Nurses and physiotherapists who work in health care institutions, primary health care services, or nursing homes can use this tool to determine the frequency of exercise undertaken by older adults, as well as their physical fitness and exercise levels and perceived exercise-related motivators and barriers. This scale can serve to measure the effectiveness of nursing interventions related to exercise, functional well-being and health promotion. Thus, older adults may maintain or achieve a better quality of life through enhanced functional capacity.

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REVIEW

Statins in cardiovascular prevention in the oldest-old. A black hole

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Elderly population is increasing rapidly together with the incidence of cardiovascular diseases (CVDs) and cardiovascular (CV) mortality. The evaluation of total CV risk is necessary for prevention of CV events, but the most used assessment tools do not include the elderly population. Among CV risk factors, hypercholesterolemia increases with the age, but the results about the association between total cholesterol (TC) levels and mortality in the elderly population are controversial. Statins are the first-choice drug for lipid-lowering therapy in the elderly due to their efficacy and safety. In primary prevention there are no recommendations to the use of statins in older adults because they do not reduce the risk of CV and all-cause mortality. On the contrary, statin treatment is recommended both in older than in younger people in secondary prevention because of the reduction of CV and all-causes mortality. High-intensity statins are more effective in the elderly population, but these dosages are associated to an increased incidence of adverse reactions, especially liver dysfunction. Finally, the degree of clinical frailty is inversely related to total cholesterol in the elderly and, accordingly, lower cholesterol levels are associated to higher mortality in this population. There are no studies that specifically evaluated the benefit of lipid-lowering therapy in severely frail older adults and a narrative-based approach, instead of an evidence-based one, has been used to choose the better treatment plan.

Key words: Cholesterol, Statins, Cardiovascular risk, Elderly

INTRODUCTION

The elderly population is rising rapidly: more than 580 million people are 60 years of age or older, and the number is estimated to increase to 1 billion by 2020. This increase in life expectancy has shifted the leading causes of death from infectious diseases to cardiovascular diseases (CVDs) and from younger to older individuals¹. In fact, CVDs account for over 80% of deaths in the elderly². All current guidelines on the prevention of CVDs recommend the assessment of total cardiovascular (CV) risk³. Among the available risk assessment

tools, the most useful and used is the Systemic Coronary Risk Estimation (SCORE) that includes a population aged between 40 and 65 years old, excluding in this way elderly people⁴. CV risk factors rise progressively with the increase of population age⁵. Moreover, several epidemiological studies have shown a high prevalence of hypercholesterolemia in later life among the CV risk factors, with Western countries having the highest prevalence⁶. However, in contrast to the expectations, only a few number of observational studies, about the relationship between total cholesterol (TC) levels and mortality in the elderly, found a U-shaped association, where high TC levels were associated with

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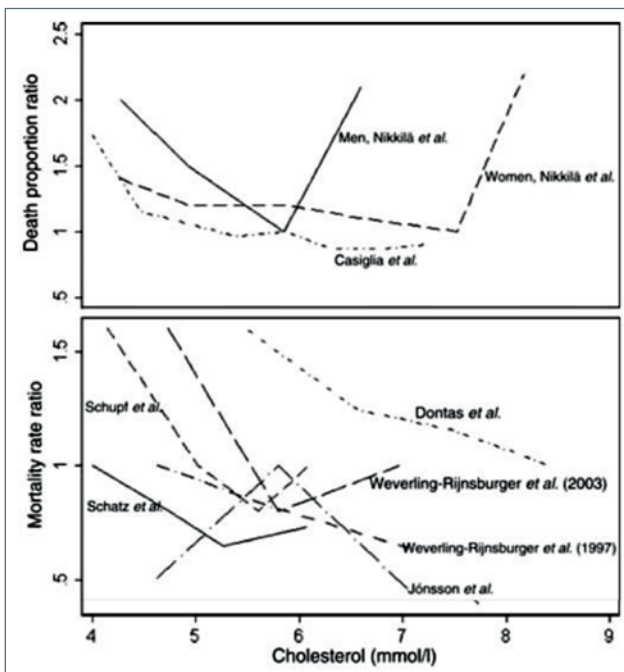


Figure 1. All-cause mortality and cholesterol in the elderly. At the x-axis, the cholesterol was plotted as an exact measure of Total Cholesterol (mmol/l). In the top panel, one study has two U-shaped plots corresponding to women and men, respectively, and one study a reverse J-shaped configuration. The middle panel showed six studies: three describing 'a reverse J-shaped configuration', two describing an almost declining curve and one study an inverted U-shaped configuration (from Petersen LK, Christensen K, Kragstrup J, 2010, mod.)⁷.

increased mortality. Most of the studies showed a J-shaped association, with highest TC levels associated to lowest all-cause mortality. Finally, low TC (< 100 mg/dl) is associated with increased mortality among > 80 years old (Fig. 1)⁷. This confused scenario shows how many complex issues are involved in the decision to whether and how introduce an effective lipid-lowering therapy in the elderly. Thus, this review summarizes the management of lipid disorders in primary and secondary prevention in the elderly.

STATINS

Statins are the drugs most extensively used for lipid-lowering therapy in the elderly, because of their efficacy, safety, and benefits through Hydroxy-Methyl-Glutaryl-CoA (HMG-CoA) reductase reversible inhibition⁸. Statins induce a reduction in cholesterol biosynthesis and, consequently, in intracellular cholesterol concentration, resulting in an increased expression of low-density lipoprotein (LDL) receptors on the surface of the

hepatocytes which leads to increased uptake of LDL-Cholesterol (LDL-C) from the blood and its decreased plasma concentration⁹. The degree of LDL-C reduction is dose dependent and varies between the different statins¹⁰. Although statins are generally well tolerated, there are adverse effects to be considered when statins are prescribed³. Muscle symptoms, such as rhabdomyolysis, myalgia and myopathy, are the most frequent, but a recent systematic review and meta-analysis about these adverse events in the elderly showed little or no evidence of a difference in risk between treatment and placebo groups¹¹. Another side effect is the hepatotoxicity, assessed by the elevations in serum concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). To date, there is not enough evidence to indicate that the incidence of hepatotoxicity or elevations of aminotransferases is higher in elderly patients receiving statins compared with younger patients¹². Statins also increase the risk of dysglycaemia and development of type 2 diabetes mellitus and this risk is higher in the elderly, especially with high-intensity statins, and in the presence of other risk factors for diabetes such as overweight or insulin resistance^{13,14}.

PRIMARY PREVENTION

Because of the lack of clinical studies or meta-analysis, European Society of Cardiology (ESC) guidelines on the management of dyslipidemia indicate IIIb class with a B level of evidence for statin therapy in oldest people without previous CV events³. One of the first primary prevention studies in patients aged > 70 years was the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) study. This study randomized 5804 patients with a mean age 75.4 ± 3.3 at high risk for CVDs to pravastatin 40 mg per day or placebo group. The primary endpoint was a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke. After 3.2 years of follow-up, pravastatin lowered LDL cholesterol concentrations by 34% and the primary endpoint by 15%. In particular pravastatin 40 mg daily reduced coronary events by 19% and coronary deaths by 24%. Although there was no effect on stroke and cognition over that period, transient ischemic attacks were reduced by 25%. The data supported the use of pravastatin in the elderly, especially given its safety and tolerability¹⁵. At the same time another primary prevention trial, the Heart Protection Study (HPS), investigated a high-risk population of 20,536 individuals, including 5806 (28%) patients aged ≥ 70 years randomized into a placebo group and a group treated with simvastatin 40 mg. The HPS divided the statins group into age groups of < 65, 65 to 69, and ≥ 70 years.

Primary outcomes were mortality (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity. Statins achieved a 24% reduction in major vascular events in the statins compared to placebo groups supporting that statins are beneficial in the elderly ¹⁶. A recent meta-analysis on the primary prevention with statins in elderly individuals at high CV risk included 8 randomized clinical trials (RCTs), enrolling 24,674 subjects and showed a reduced risk of myocardial infarction (MI) by 39.4% compared with placebo (Relative Risk: 0.60 [95% Confidence Interval: 0.43 to 0.84]) and stroke by 23.8% compared with placebo (Relative Risk: 0.76 [95% Confidence Interval: 0.62 to 0.92]). However, statins did not significantly reduce the risk of all-cause death compared with placebo (Relative Risk: 0.94 [95% Confidence Interval: 0.85 to 1.03]) and the risk of CV death (Relative Risk: 0.90 [95% Confidence Interval: 0.68 to 1.19]) ¹⁷.

Also the US Preventive Services Task Force (USPSTF) Recommendation Statement establishes indication to statin therapy in adults aged 40-75 years with no history of CVD, ≥ 1 CVD risk factors, and calculated 10-years CVD event risk ≥ 10% or 7.5-10% with a Grade of Certainty B and C respectively. However, it also establishes

that there is no recommendation to the use of statins in adults 76 years and older with no history of CVD with a Grade I of Certainty, that corresponds to insufficient current evidences to assess the balance of benefits and harms of the treatment ¹⁸.

Finally, statin therapy is not directly recommended for primary prevention in the elderly because they only reduce the risk of CV and cerebrovascular events, but not CV and all-cause mortality. Because of the lack of evidence in this population, a possible approach could be based on “start low and go slow”: starting from a lower dosage and increasing it progressively, also in function of the onset of any side effects.

In Table I are indicated most of the “primary” prevention studies described above.

SECONDARY PREVENTION

ESC guidelines on the management of dyslipidemia assigns to statin treatment in older adults with established CVDs a Class I and Level of Evidence A, as for younger patients ³. A meta-analysis on the use of statins in elderly individuals for secondary prevention collected data from 18 double-blind RCTs of statins vs. placebo

Table I. Summary of major statin studies involving elderly patients.

Author	Year	Type of study	Prevention	Age	Results
Shepherd et al. ¹⁵	2002	RCT	Primary	75.4 ± 3.3	Pravastatin 40 mg daily given for 3 years reduces the risk of coronary disease in elderly patients.
Heart Protection Study Collaborative Group ¹⁶	2002	RCT	Primary	40–80 years 28% patients aged ≥ 70 years	Long-term simvastatin 40 mg daily reduces the rates of myocardial infarction, stroke and revascularization in high-risk populations independently of age.
Cannon et al. ²⁴	2004	RCT	Secondary High-intensity vs. moderate intensity	58.3±11.3 30% patients aged ≥ 65 years	High-intensity statin regimen provides greater protection against death or major CV events than standard regimen (pravastatin 40 mg) in younger but also in elderly patients.
Deedwania et al. ²⁵	2007	RCT	Primary and secondary prevention High-intensity vs. moderate intensity	72.6 ± 5.2	High intensity statin therapy (atorvastatin 80 mg) is associated with major reductions in cholesterol, major acute CV events and death than moderate-intensity statin (pravastatin 40 mg) in elderly patients.
Ridker et al. ²³	2008	RCT	Primary	66 (median) 32% patients aged ≥ 70 years	Rosuvastatin 20 mg significantly reduces the incidence of major CV events both in younger than in older patients without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels.
Chaturvediet al. ²²	2009	RCT	Secondary	72.5 ± 0.2	Aotrvastatin 80 mg reduces the incidence of CV events both in younger than in older patients, but it reduces the incidence of cerebrovascular events (stroke and TIA) only in younger patients.

RCT: Randomized Controlled Trials; CV: Cardiovascular

accounting 51.351 persons of which 31.633 (62%) were aged 60 years or older. This meta-analysis showed that statins reduced all-cause mortality by 15% (Relative Risk: 0.85, 95% Confidence Interval: 0.78-0.93), coronary heart disease (CHD) death by 23% (Relative Risk: 0.77, 95% Confidence Interval: 0.71-0.85), fatal or nonfatal myocardial infarction by 26% (Relative Risk: 0.74, 95% Confidence Interval: 0.70-0.78) and fatal or nonfatal stroke by 24% (Relative Risk: 0.76, 95% Confidence Interval: 0.65-0.90)¹⁹. Another meta-analysis showed that the proportional reduction in the incidence of coronary revascularization per 1.0 mmol/L reduction in LDL cholesterol was significantly larger in the trials of more vs. less intensive therapy than in those of statins vs. control not only in subjects aged 65 or less, but also in those aged 65-75 or more (Fig. 2)²⁰.

Nevertheless, a very recent “Quasi-experimental study” (i.e. no randomization trial) evaluated the safety and effectiveness of statin treatment for secondary prevention in 12.156 older patients divided in two groups of 6.078, one of control and one in treatment with statins, regardless of strength and treatment duration. Statins were associated with protective effect in the 60-79 age group (Hazard Risk: 0.73, Confidence interval: 0.57-0.94) but showed a non-significant result in the ≥ 80 group (Hazard Risk: 1.06, Confidence interval: 0.78-1.44). Data also suggest an increased risk of falls (Hazard Risk: 1.36, Confidence interval: 1.17-1.60) and fractures (Hazard Risk: 1.33, Confidence interval: 1.04-1.69) in the first 2 years of treatment, particularly in the ≥ 80 group. Treatment was also associated with lower all-cause mortality (Hazard Risk: 0.62, Confidence interval: 0.57-0.68)²¹. The results of this study were similar to other trial and meta-analysis results as regards to statins effectiveness for the secondary prevention in patients aged 60-79

years. Unfortunately, the reduction of CV events, in particular myocardial infarction, in the group of patients aged 80 years and older, is not statistically significant and it also shows a significant increase in the risk of falls and fractures in this group. Although this study is performed with a “Quasi-experimental” method, it raises questions that require further investigation.

Actually, statin therapy is strongly recommended for secondary prevention in elderly population as well as in younger people because of the reduction of CV and all-cause mortality. However, evidences in patients older than 80 are poor.

In Table I are indicated most of the “secondary” prevention studies described above.

HIGH-INTENSITY STATINS AND ADVERSE EVENTS

Atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg are defined high-intensity statins. Among the major studies involving elderly patients, only JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) studies used high-intensity statins. In particular, SPARCL evaluated the risk of recurrent fatal and nonfatal stroke in a cohort of 4731 patients aged ≥ 65 years with a history of prior stroke or transient ischemic attack (TIA) randomized to atorvastatin 80 mg or placebo, in order to evaluate whether this class of patients had the same benefit from statin treatment as younger patients. The SPARCL study showed a statistically significant reduction of any cardiovascular event and stroke or TIA in younger patients ($p = 0.00360$; $p \leq 0.0001$ respectively), but a statistically

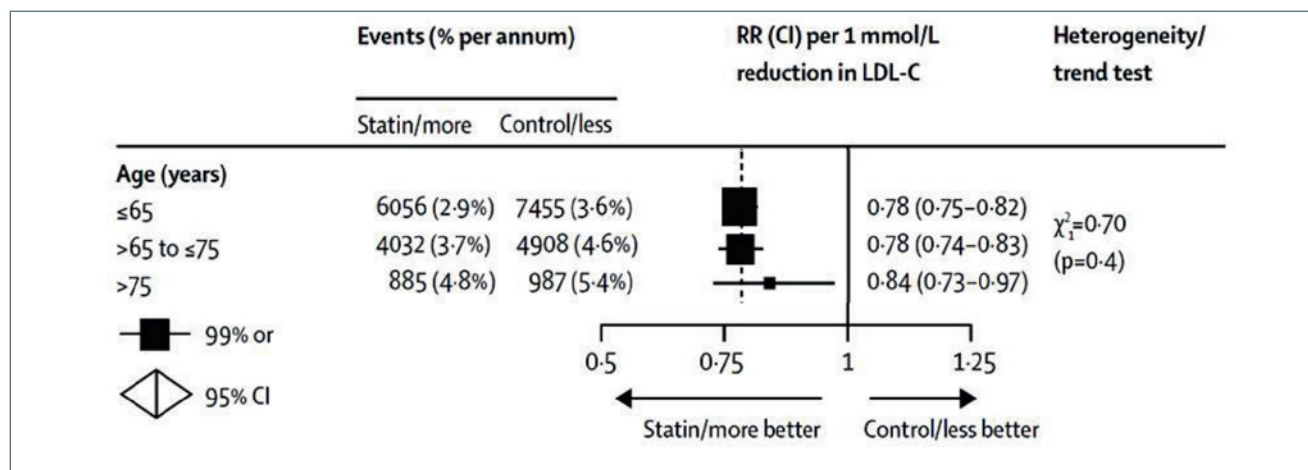


Figure 2. Risk ratio for all-cause mortality from 14 studies of secondary prevention with statins in the elderly. Note that the statins' protective effect decreases from 65-7 to ≥ 75 years old (from Cholesterol Treatment Trialists' (CTT) Collaboration, mod.)²⁰.

significant reduction of only any CV event in the older cohort but not of stroke and TIA ($p = 0.0005$; $p = 0.2643$ respectively)²². The JUPITER trial assessed the efficacy of rosuvastatin 20 mg vs placebo in primary prevention. In this trial 32% of participants were aged ≥ 70 years. The primary outcome was the occurrence of a first major CV event, defined as nonfatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. Secondary endpoints included the components of the primary endpoint considered individually and death from any cause. Patients who received rosuvastatin had significantly lower rates of both primary and secondary endpoints when compared with patients on placebo²³. In both these studies the occurrence of serious adverse events between the two groups was not statistically significant, regardless of the age.

There are only two studies comparing high-intensity with intermediate-intensity statins: PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) and SAGE (Study Assessing Goals in the Elderly), which is the only conducted entirely in the elderly. PROVE IT-TIMI 22 trial was designed to compare the efficacy of pravastatin 40 mg vs atorvastatin 80 mg with a LDL-C goal of 70 mg/dL and a primary endpoint of secondary prevention of death or major cardiovascular events. In this study 30% of patients were aged ≥ 65 years. The study showed a statistically significant reduction of LDL-C in the atorvastatin group than in the pravastatin group (62 mg/dl vs 95 mg/dl; $p < 0.001$). Kaplan–Meier curves showed a reduction of the rates of the primary endpoint at two years of 26.3% in the pravastatin group and 22.4% in the atorvastatin group, reflecting the superiority of the more intensive regimen vs the standard one ($p = 0.005$) with same results for older and younger patients²⁴. The SAGE study examined differences in the occurrence of episodes of myocardial ischemia in elderly patients aged between 66 to 85 years receiving intensive vs moderate statin therapy (atorvastatin 80 mg vs pravastatin 40 mg, respectively). Atorvastatin-treated patients experienced greater LDL reductions, fewer major acute cardiovascular events (Hazard Ratio = 0.71; 95% Confidence Interval, 0.46, 1.09; $p = 0.114$), and a significantly greater reduction in all-cause death (Hazard Ratio = 0.33; 95% Confidence Interval, 0.13, 0.83; $p = 0.014$) than pravastatin-treated patients²⁵. In both these studies the rate of adverse events was similar between the 2 treatment groups with the exception of liver dysfunction, defined as ALT or AST > 3 times the upper limit of normal, that was more frequent in the atorvastatin than in the pravastatin group in SAGE (4.3% vs 0.2% respectively, $p < 0.001$) and in PROVE IT-TIMI 22 (3.3% vs 1.1% respectively, $p < 0.001$).

As regards the risk of cancer related to the use of statins, meta-analyses above mentioned^{17–19} showed the absolute absence of statistically significant correlation. In a meta-analysis about cancer risk in older people receiving statin therapy, 12 RCTs involving 62,927 patients (31,517 in statin therapy group and 31,410 in control group) were analyzed showing that neither the variety nor the chemical properties of the statin therapy did not affect the overall incidence of cancer (Odds Ratio: 1.03, 95% Confidence Interval: 0.94–1.14, $p = 0.52$) in this population²⁶.

ELDERLY PARADOX

An analysis of the results of the above mentioned JUPITER study shows a relative risk reduction as a percentage from treatment with rosuvastatin compared with placebo higher in younger patients than in older patients both for the primary and the secondary endpoint. However, a reduction in the absolute risk was higher in older than in younger patients²⁷.

Although these results may seem contradictory and may suggest an ineffectiveness of the statin treatment in the elderly, this phenomenon is defined “elderly paradox” and it is very frequent in intervention trial in older populations. This phenomenon is clearly explained in Fig. 3. If you consider the absolute reduction of mortality in “adult” patients (from $n = 10$ to $n = 6 = n - 4$), the relative reduction is 40%. In contrast, as mortality in elderly patients is higher, the absolute reduction of mortality in “elderly” patients is higher (from $n = 20$ to $n = 15 = n - 5$), but the relative reduction is lower (25%). Therefore, the number of patients needed to be treated (NNT) to prevent an event is less in the elderly ($100/20 = 5$) when compared to adult ones ($100/25 = 4$).

COMORBID/FRAIL ELDERLY

Frailty is currently defined “primary” or “pre-clinical” when the state is associated with a vulnerability state²⁸, and “secondary” or “clinical” when it is associated with known comorbidity and/or disability²⁹. The characteristics of clinical frailty include not only comorbidity and disability but also polypharmacy and relative adverse drug reactions, hospitalization, health service utilization, age-associated sensory deficits, and lack of social support^{30–31}. The concept of frailty helps to identify elderly patients most susceptible to adverse outcomes, such as loss of independence, hospitalization and death, alone and in association with chronic disorder such as chronic heart failure³². Very interestingly, it has been recently showed that the degree of clinical frailty



Figure 3. Elderly paradox (see text for the explanation).

is inversely related to TC in the elderly and the value less of 100 mg/dl is related to the highest frailty index (Fig. 4)³³. Accordingly, as indicated before, several studies showed a “U” curve mortality-related total cholesterol indicating that very low and very high cholesterol levels are associated to higher mortality^{7 34-36}. In particular the concomitant presence of low blood pressure, low body mass index and low serum TC is associated with higher mortality in the elderly, leading to a new phenotype, i.e., “reverse metabolic syndrome”³⁷. In contrast, in 2597 community-dwelling patients aged ≥ 65 years with a previous hospitalization for coronary artery disease assessed with the Multidimensional Prognostic Index (MPI), based on the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (SVaMA), higher 3-years mortality rate was associated with lower rates of statin treatment³⁸.

These findings, together with the lack of studies specifically evaluating the benefit of lipid-lowering therapy in severely frail older adults, may encourage the definition of controlled studies on the use of statins in this group of patients^{39 40}.

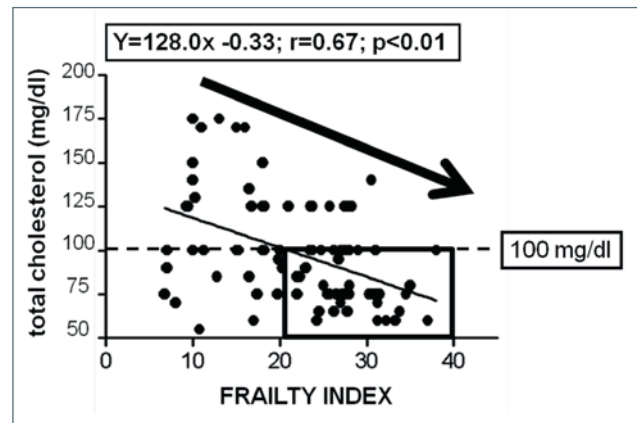


Figure 4. Total cholesterol is inversely related to clinical frailty evaluated by “Frailty index” (from Abete et al., 2017, mod.)³³.

CONCLUSIONS

- Statin therapy should be considered in older adults in primary prevention, particularly in the presence of cardiovascular high risk pattern (i.e., hypertension, smoking, diabetes and dyslipidemia);

- treatment with statins is recommended for older adults in secondary prevention in the same way as for younger patients;
- at high dosage statins should be used with great caution since older people often have comorbidities that may determine the stop of the therapy (10%);
- particularly attention for older than 75 years and comorbid/frail elderly patients in whom evidence-based medicine is limited.

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REVIEW

The interplay between fascia, skeletal muscle, nerves, adipose tissue, inflammation and mechanical stress in musculo-fascial regeneration

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Muscle and connective tissues are structures that provide stability and movement to organisms belonging to the animal kingdom. Fascia and muscle tissues structurally and functionally integrate to form a musculofascial system with exceptional biomechanical properties, which allow animals to accomplish complex tasks. Mechanical overload through intense exercise or injury, however, may damage these tissues over the course of a lifetime. Although mammalian skeletal muscle and fascia both retain a good regenerative potential in the adulthood, regeneration is very sensitive to alterations in the biochemical and physical environment. In this review, the reciprocal role of fascial tissue and skeletal muscle in their regeneration processes are explored. The involvement of adipose and nervous tissue in the regulation of muscle and fascia regeneration are also revised. It is hypothesised, for the first time, that for effective regeneration of skeletal muscle, both muscle and fascial tissues are necessary, and that nervous and adipose tissues contribute and deeply influence this process.

Key words: Skeletal muscle, Fascia, Musculo-fascial regeneration, Extracellular matrix, Muscle loading, Muscle innervation, Intramuscular adipose tissue

INTRODUCTION

Mammalian skeletal muscle has a complex structure composed by different elements, such as myofibres, connective tissue, blood vessels, nerves, adipose cells and immune cells. Trauma, such as strain injuries, which are very common in sport, damage the muscles. Moreover, chronic degenerative neuromuscular diseases, forced inactivity, and aging can significantly impair muscle structure, mass and functionality¹. Damaged skeletal muscle can regenerate through the coordinated action of different cells and mechanisms, but this process is very complex and unfavorable factors can lead to ineffective muscle repair. Much has been

already understood about skeletal muscle regeneration, but many of its aspects, such as the contribution of fascia, nerves, and adipose tissue still remain poorly investigated.

STRUCTURE OF FASCIAL TISSUE

Fascia is a fibrous connective tissue, which envelopes and infiltrates all the organs and structures of the human body, including muscles, vessels, nerves, and joints². Although the gross anatomical structure of fascia varies throughout the human body, all fascial tissue is composed of cells and an extracellular matrix (ECM).

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FASCIAL CELLS

The main cell types within fascia include fibroblasts, myofibroblasts, fibrocytes, adipocytes, telocytes and migrating white blood cells³⁻⁵. Fibroblasts are mesenchyme-derived cells that produce ECM, release cytokines, and can be transformed, under the certain stimuli, into myofibroblasts⁶. Myofibroblasts express α smooth muscle actin (α SMA) and myosin and have contractile properties⁷. Myofibroblasts, therefore, have the capacity to generate tension in the surrounding ECM, and in addition to secreting cytokines, can also migrate, and respond to chemokines⁸. Fibrocytes are monocyte-derived cells that have features of both macrophages and fibroblasts⁷. Fibrocytes migrate into the injured tissue, where they can differentiate into macrophages or into fibroblasts/myofibroblasts⁷. Adipocytes are connective-tissue cells that store and synthesize fat, and white blood cells belong to the immune system. Telocytes are interstitial cells with mechanotransduction features, which are involved in inter-cellular signaling, survival of satellite cells, angiogenesis, and maintenance of tissue homeostasis. These specific properties of telocytes, make them key elements for tissue regeneration^{9,10}.

FASCIA ASSOCIATED WITH SKELETAL MUSCLE TISSUE

Fascia and muscle tissue strictly cooperate to achieve the higher-order function of the whole human body. The fascia of the muscle tissue can be divided into a superficial fascia, a denser deep fascia, which includes muscular septi (like the lateral septum of the upper arm) and a muscle-specific fascial tissue, which includes three different layers: epimysium, perimysium, and endomysium².

Each of these muscle-specific fascial layers has a different molecular and structural composition¹¹. Endomysium, which envelopes myofibers, contains a matrix layer and a particular structure, the basement membrane. The matrix layer is formed by collagen type I, FN, HA, chondroitin sulfate and dermatan sulfate proteoglycans^{12,13}. The basement membrane is composed mainly of matrix proteins; laminins, type IV and VI collagen, nidogens and the HSPG perlecan¹⁴. These proteins are organized in highly specialized and complex networks that make contacts with integrins and dystroglycan on the surface of myofibers^{13,15,16}. Perimysium, which separates muscle fascicles, is associated with a reticular network composed of collagen fibers, through which it controls the number of mitochondria in the subsarcolemmal space. Epimysium is a thick

collagenous sheath that extends from the tendons and envelops many muscle fascicles. Endomysium is a thin layer of connective tissue that surrounds every single muscle fibre. Epimysium, perimysium, and endomysium are predominantly constituted by collagen type I, II and III, which is synthesized by fibroblasts¹⁷. Cells, via integrins, and extracellular- and basement-membrane proteins, therefore, participate in the formation of a complex 3D network within and surrounding muscle tissue¹⁸.

Fascia acts as a mechanical bridge between different tissues. It transfers mechanical stress, which originates in a specific point of the body, to different areas and tissues. This force transmission allows these different body regions to sense the tensile stimulus and activate proprioceptors and mechanoreceptors¹⁹. Interstitial connective tissue contains and support blood vessels, nerves, and lymphatic tissue, and is responsible for the transfer of mechanical force from the muscle to the skeleton²⁰. Nevertheless, fascia is not just a passive force transmitter. It also regulates mechanical stress by adsorbing, storing and releasing kinetic energy².

The main structural component of fascia, the ECM, reflects the biomechanical environment of muscle tissue, with a structural and a functional role that is based on its constituting proteins: laminin, entactin, fibrinogen, types I and VI collagen, and vitronectin^{21,22}. The ECM of fascia not only provides mechanical support to the muscle, but is also fundamental for the transduction of mechanical tension to muscle cells and of muscle contraction to the surrounding tissues¹¹. At the molecular level, this efficient mechanical communication between different tissues is achieved by means of the ECM, cellular membrane receptors linked to the ECM fibers, and cytoplasmic/cytoskeletal proteins linked to membrane receptors¹¹.

The ECM also governs cell orientation and organization²³ and enhances muscle regeneration by regulating muscle cell proliferation, migration, fragmentation and fusion²⁴. Another important function of the ECM is the regulation of growth factor activity during muscle regeneration, through protein-protein interactions¹⁸. Pathologic changes in the ECM, such as fibrotic ECM, can reduce the regenerative potential of muscle fibers, independently of the myogenic potential itself²⁵. The role of the ECM in maintaining tissue and cellular stability is also highlighted by the phenomenon called anoikis; a programmed cell death process (apoptosis) arising from the interruption of the interaction between ECM and adjacent cells²².

There is a constant balance between the amounts of connective tissue and parenchyma in any tissue²⁶. Healthy skeletal muscle has a high volume ratio of muscle cells to fibroblasts, with fibroblast nuclei comprising

8-15% of all nuclei in the tissue²⁷. For normal tissue turnover, cells also release enzymes that degrade the ECM, such as cathepsins, heparanase, hyaluronidases, and metalloproteinases (MMPs)²². Excessive accumulation of connective tissue, in the form of collagen fibers and myofibroblasts, leads to muscle fibrosis, and diseases, such as Dupuytren Disease²⁸⁻³⁰.

EXTRACELLULAR MATRIX

The ECM fills the extracellular space both within and between each tissue, thus forming the interstitial connective tissue, where it acts as a structural scaffold and functional regulator²². The principal components of the ECM are structural proteins (collagens, laminins, fibronectin, vitronectin, tenascin-c, and elastin), specialized proteins (growth factors, small matricellular proteins and small integrin-binding glycoproteins (SIBLINGS)), glycosaminoglycans and proteoglycans, such as metalloproteinases and cytokines, and water¹⁴. Although the precise composition of the ECM varies between different tissues, collectively the proteins of the ECM confer adhesion, strength, and elasticity to fascial tissues¹⁸. Moreover, they also play an important role in inter-cellular signaling, due to their capacity to store and release growth factors, such as TGFs, and IGFs¹⁴.

STRUCTURAL PROTEINS

Fibronectin (FN) binds to several ECM molecules, including collagen and tenascin, and promotes cell adhesion and migration¹⁴. Also, FN binding to integrins is a crucial step in the fibril assembly process¹⁸. Tenascin C regulates the activity of integrins and syndecan and has a fundamental role in muscle innervation and neural function¹⁴. Elastin forms polymeric elastic fibers that cross-link in an extensible 3D network, which moderate the extensibility of tissues when exposed to low-level force. Collagen is a collective term commonly used to refer to a family of structural proteins of the ECM that provide resistance to tension and link together different ECM proteins. The fibrous components of fascia mainly consist of types I, III, IV, V, VI, XI, XII, XIV, XXI collagen⁴. Vitronectin is an adhesion protein binding cells to the ECM. Laminins, on the other hand, bind to integrins and the dystrophin-glycoprotein complex (DGC)¹⁵.

SPECIALIZED PROTEINS

The ECM is linked to cells by means of adhesion proteins (e.g. integrin receptors, mechanosensitive ion channels and tyrosine kinases), localized on the cell membrane and acting as a bridge between ECM fibers and the intracellular cytoskeleton. Integrin receptors bind to laminins, collagens, fibronectin, tenascin and

link ECM proteins to the intracellular environment, via interaction with actin. This organization enables a fast mechanical communication between the extracellular and the intracellular environments¹⁵. Upon receiving a mechanical input, cells can modify their morphology, 3D orientation, and activity. Therefore, tissue restructuring can be influenced by mechanical stress²⁶.

GLYCOSAMINOGLYCANS AND PROTEOGLYCANS

Heparan sulfate proteoglycans (HSPGs) are components of the ECM and the basement membrane of skeletal muscle. HSPGs form multimeric fibrils and bind to many proteins in the ECM, such as FGF-2, thanks to their negative charges¹⁴. Glycosaminoglycans confer gel properties to the ECM and act as important storage system for growth factors and cytokines²¹. Hyaluronan (HA) is a linear polysaccharide whose main function is to provide lubrication, hydration, and resistance to compression³¹. It is also present as in an aggregated form, which increases the viscosity of ECM and reduces the gliding of connective and muscle tissue layers³².

STRUCTURE OF SKELETAL MUSCLE TISSUE

In mammals, skeletal muscle can account for up to 40% of the total body mass, thus representing the most abundant tissue. It maintains posture and enables voluntary body movements under the control of the cortical areas of the central nervous system.

Skeletal muscle is defined as “striated” muscle because of its band-patterned appearance under microscopic examination³³. Muscle fiber is the smallest functional unit of skeletal muscle. It is a long, multinucleated cylindrical cell composed of a large number of contractile elements, the myofibrils. Skeletal muscle is composed of hundreds to thousands of multinucleated muscle fibers. Many individual muscle fibers are bundled in fascicles by a layer of connective tissue, the endomysium. Fascicles are grouped, in turn, in the muscle by a sheet of connective tissue, the perimysium. Two more connective tissue layers, the epimysium, and the deep fascia, wrap the muscle and separate it from other muscles, respectively³⁴.

Muscle cells establish a connection to the ECM via dystrophin- and integrin-associated complexes^{15 35 36}. These junctions allow the transmission of mechanical traction generated by muscle fibers to the ECM. Another important filament-like protein that contributes to the formation of the bridge between the extracellular matrix and the cytoskeleton of muscle cells is syncoilin³⁷. This protein belongs to the dystrophin-associated protein complex and is localized to the sarcolemma of muscle fibers³⁷. Studies on mice have demonstrated

that Syncoilin is fundamental for the lateral transmission of muscle tension to the extracellular environment³⁷. Disease, forced inactivity, injury, malnutrition, and aging can significantly, and dangerously, deplete the mass and functionality of muscles³⁸. The potential of natural or induced skeletal muscle repair is crucial to re-establish tissue integrity after muscular injury.

REGENERATION OF MUSCLE AND FASCIAL TISSUE

To preserve body integrity and function, both fascia and skeletal muscle tissues act synergistically to aid each other in regeneration. In fact, previous studies have shown that both satellite cells and resident fibroblasts are fundamental for effective regeneration of connective tissue and muscle (Fig. 1). In particular, fibroblasts can enhance satellite cell proliferation and self-renewal³⁹, and skeletal muscle cells participate in the rebuilding of connective tissue¹⁴.

The ECM is a central player in muscle development and regeneration. It is a very dynamic structure that constantly adapts to the environment by continuously switching between degradation and re-assembly. It influences cell proliferation, survival, shape, migration, and differentiation. No wonder its alteration may lead to disease¹⁸.

Metalloproteinases (MMPs) and A Disintegrin and Metalloprotease (ADAMs) are proteases involved in the degradation of ECM proteins. MMPs are produced intracellularly as inactive precursors and are activated by extracellular proteolytic activity. ADAMs, in contrast, are transmembrane proteins located on the membrane of muscle cell¹⁴. The balanced control of MMP activity is achieved by the secretion of tissue inhibitors of MMPs (TIMPs) that allow MMP action to be finely tuned¹⁴. Proteolytic degradation of the ECM is also a crucial step for the movement of endothelial cells during regenerative neovascularization⁴⁰. ECM degradation, therefore, not only destroys the extracellular protein network but also generates bioactive peptides and releases growth factors trapped within the ECM¹⁸.

Given the strong interconnection between ECM and skeletal muscle, it is not surprising that skeletal muscle influences the remodeling of the ECM. In fact, during skeletal muscle regeneration extracellular proteases (MMP-2, MMP-7, MMP-9, MMP-24, MMP-25, plasmin and the plasminogen activation system), secreted by muscle cells, inflammatory cells and other cells, participate in the degradation of the ECM⁴¹. MMPs can both degrade ECM proteins, such as collagen fibers, elastin, proteoglycans, and fibronectin as well as proteolytically activate other proteins, such as the MMPs

themselves⁴². For example, plasmin can degrade fibronectin and laminin and also activate MMPs and several latent growth factors⁴³. Moreover, there is some evidence that activated satellite cells influence the remodeling of ECM^{14,25}.

The formation of new muscle mass is a process involving muscle cells and non-muscle cells with myogenic potential, such as adipose-tissue derived stem cells, mesoangioblasts, pericytes, side-population cells, Ac133 + cells, stem and/or precursor cells from muscle endothelium, and synovium⁴⁴. Nevertheless, skeletal muscle regeneration relies mainly on the activity of satellite cells, i.e. muscular stem cells (MuSCs) with asymmetric division and self-renewal capabilities⁴⁵. These cells are small, have a single nucleus, and are located between the myofiber sarcolemma and the basal lamina, and are, therefore, in close contact with the ECM. The paired box 7 (Pax7) transcription factor and tetraspanin KAI/CD82 are the molecular markers that identify satellite cells^{46,47}. Pax7+ satellite cells are capable of asymmetric division, thus contributing to the regeneration of muscle fibers and, at the same time, maintenance of the stem cell pool⁴⁸. Furthermore, MuSCs express different molecular markers in the quiescent state and the proliferating/differentiating state⁴⁶. Even though satellite cells constitute the vast majority of MuSCs, it has been observed that non-satellite cells like mesenchymal stem cells may also acquire the skeletal muscle features under appropriate conditions⁴⁹. Upon skeletal muscle injury, satellite cells are activated and start proliferating to execute the dual program of self-renewing and differentiation into new muscular fibers⁵⁰. The critical balance between post-replicative differentiation and stemness is regulated by the presence of myogenic and self-renewing subpopulations of satellite cells⁵¹. On the other hand, the satellite niche, which is the MuSCs microenvironment, provides specific signals driving satellite cells toward either differentiation or stemness fate⁴⁶. These signals include cell-to-matrix and cell-to-cell interactions, autocrine and paracrine stimuli, as well as other biochemical factors.

Satellite cells live in a reversible 'G0' or quiescence state that is crucial for the maintenance of the pool of myogenic precursors. This state allows satellite cells to re-enter the cell cycle in response to specific stimuli, like muscular injury. Cell cycle entry and exit are controlled by the coordinated expression of an array of regulatory genes and factors. While genes inhibiting the cell cycle are highly expressed in quiescent satellite cells, those promoting the cell cycle are activated after muscular injury⁵²⁻⁵⁵. During muscle regeneration, proliferating satellite cells either exit the cell cycle to return to a quiescent state and restore the MuSC pool or, alternatively, differentiate into myoblasts and fuse with pre-existing

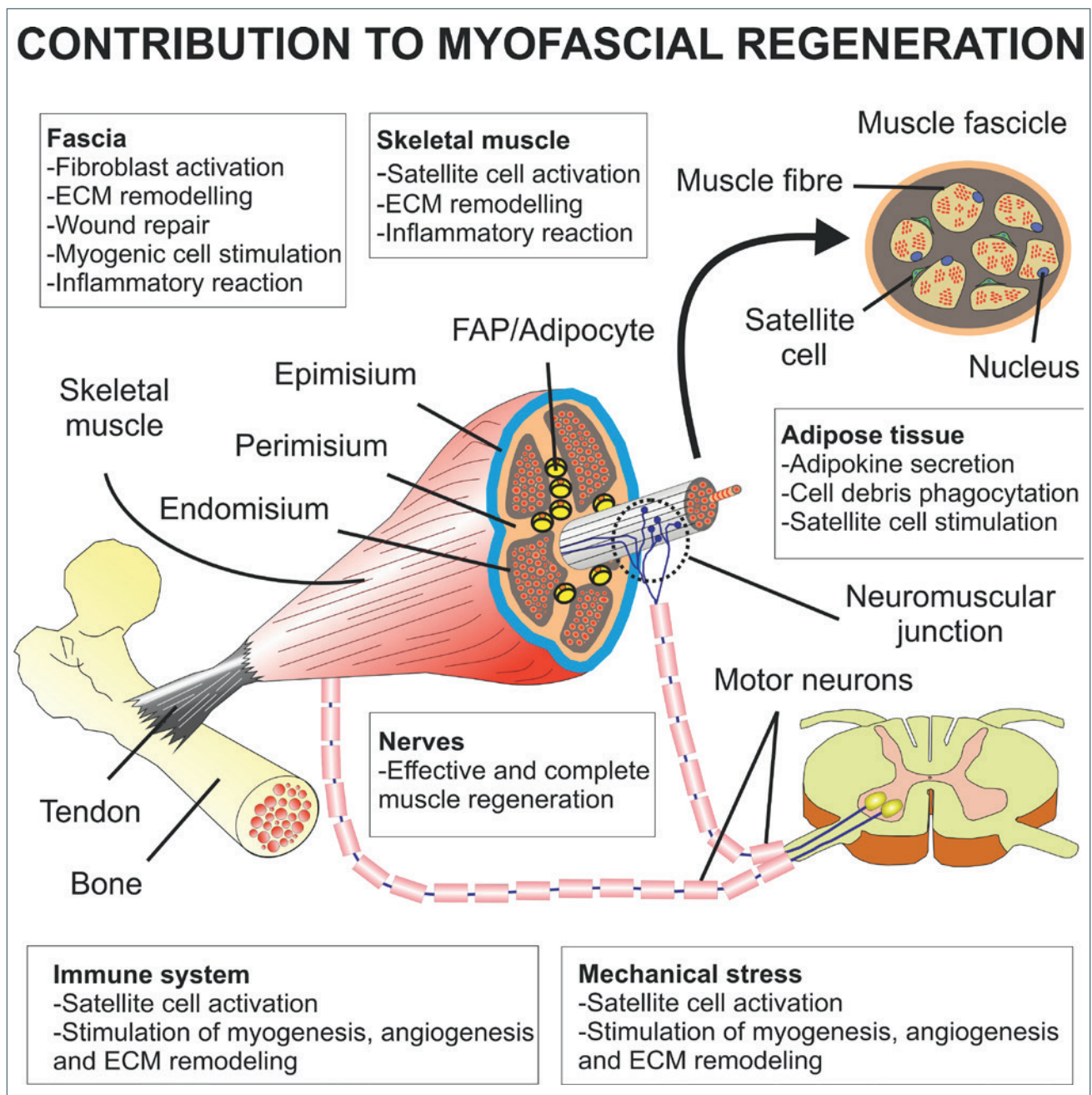


Figure 1. Scheme showing the contribution of skeletal muscle, fascia, nerves, intramuscular adipose tissue, immune system, and mechanical stress to myofascial regeneration.

muscle fibers to form new myofibers^{56,57}. Collagen type VI, present in the ECM, and fibronectin, produced by activated satellite cells, induces the self-renewal of the satellite pool^{58,59}. The post-mitotic cellular contacts within the niche also play a role in the determination of the satellite cell fate. For example, daughter cells in contact with the basement membrane are directed to the satellite cell self-renewal pathway, while daughter

cells interacting with myofibers differentiate into myofibers⁶⁰.

ECM components also enhance muscle regeneration by regulating muscle cell proliferation, migration, fragmentation, and fusion²⁴. Aberrant ECM remodeling after muscle injury, therefore, leads to ineffective muscle regeneration⁶¹. In the initial phase of skeletal muscle regeneration, both fibroblasts and satellite cells actively

proliferate, promoting each other's growth through a reciprocal positive feedback³⁹.

Cellular activities, as well as temporal and spatial production of ECM proteins, vary according to the different phases of the regeneration process¹⁴. Following tissue injury, fibroblasts migrate to the site of damage, proliferate and generate an extracellular network of disorganized collagen III fibers, most of which are subsequently transformed into collagen I fibers. Moreover, fibroblasts also secrete growth factors for the myogenic cells and differentiate into myofibroblasts, which contribute to the formation of new muscle fibers³⁹. At this stage, the ECM collagen type I/III, which confer tensile strength, and laminin, tenascin-C, and fibronectin, which confer elastic properties, are produced, and TGF- β 1 is one important driver of such processes⁶². After this phase, a wound contracture process shortens the edges of the damaged area⁶³. The shortening of these margins takes place because of the crosslinking and shortening of the collagen fibers. As result, a tight scar forms, thus increasing the mechanical resistance, and the functional performances of the damaged tissues. Afterward, collagen fibers aggregate and orientate to give better functional responses to mechanical stress, and to contractile activity⁶³. This fibrotic response is beneficial in the initial phase of tissue regeneration because it preserves the tissue integrity. On the other hand, fibrotic elements should be removed, little by little, from the injured site, to replace the fibrotic tissue with functional skeletal muscle tissue⁶².

During the regenerative phase, the regrown myofibers establish new and stronger lateral contacts (increasing the numbers of integrins on the adhesion sites) with the surrounding ECM, to allow some muscle activity and reduce the risk of a re-rupture¹⁴. The role of ECM in regenerative processes is so important that it has also been demonstrated in nonmammalian animal models, such as axolotl and *Octopus Vulgaris*^{64 65}.

ADIPOSE TISSUE

There is a close physical and biochemical link between connective tissue, muscle tissue, and adipose tissue. Therefore, they profoundly influence each other. In particular, skeletal muscle activity and regeneration are strongly affected by adipose tissue. Adipocytes are present in muscle tissue as "intramuscular fat", and secrete adipokines, proteic hormones that also regulate skeletal muscle development and function (Fig. 1).

Different cell types, including mesenchymal progenitors and fibro/adipogenic progenitors (FAPs), have been shown to participate in the development of fat cells within the muscle tissue, however, the potential of

satellite cells to generate intramuscular adipocytes has only been suggested⁶⁶. FAPs are multipotent mesenchymal progenitor cells that are present in many tissues, such as skeletal muscle. These cells are fundamental in the process of muscle regeneration. In fact, after muscle injury, they transiently proliferate, phagocytize necrotic debris, and stimulate satellite cell expansion. Importantly, after this initial phase, the number of FAP must rapidly decline to allow efficient muscle regeneration^{67 68}. Under disuse or chronic muscle diseases, such as dystrophic conditions, FAPs proliferate, differentiate into adipocytes and ECM-producing fibroblasts and persist in the tissue; thereby resulting in the accumulation of intra-muscular adipose tissue (IMAT) and fibrotic tissue⁶⁹⁻⁷¹. In particular, FAPs can be induced to differentiate into ECM-producing cells by macrophages⁷². It has been shown in mouse models, that unloading inhibits IMAT accumulation in regenerating muscle⁷³. The accumulation of fat tissue in the muscle inhibits its regenerative potential because it suppresses the proliferative capacity of satellite cells and may also inhibit the activity of macrophages^{73 74}. In fact, obese mice have a very low skeletal muscle regenerative potential⁷⁴. Fatty infiltration in the muscle tissue has also been proposed to arise from the differentiation of FAP into adipocytes when muscle regeneration is impaired⁶⁷. The crosstalk among MuSCs, FAPs, and immune cells determines the fate of the muscle tissue; either toward regeneration or fibro-adipogenic degeneration⁷⁵.

In vitro, adipose stem cells can influence the activity of myofibroblasts. In particular, this cell-cell interaction leads to inhibition of actin expression and contractility in smooth muscle⁷⁶. In the rat, it has been demonstrated that adipose tissue-derived regenerative cells (ADRCs) can stimulate the repair of injured skeletal muscle tissue, through their paracrine activity⁷⁷. In particular, these cells promote angiogenesis and myogenesis and prevent fibrosis. Moreover, adipose-derived stem cells (ASCs) have been shown *in vitro* to differentiate into skeletal muscle cells⁷⁸. Experimental evidence has also demonstrated that human ADSC can be transdifferentiated into fibroblast-like cells *in vitro*⁷⁹. These observations underline the close interconnection between adipose and connective tissue.

The interaction among different tissues also relies on soluble factors that are released from one tissue and target other tissues. Adipose tissue, once believed to be merely an energy depot, secretes an extensive repertoire of molecules, collectively called adipokines, which can affect surrounding cells or distant cells, thus acting in a paracrine or endocrine fashion. Skeletal muscle expresses receptors for several adipokines, including adiponectin and leptin⁴⁴. Globular adiponectin (gAD) is also involved in the proliferation and myogenic

differentiation of satellite cells, myoblasts, and mesoangioblasts⁴⁴. gAd is also fundamental for the migration of satellite cells and macrophages towards the muscle tissue. Moreover, gAD causes the degradation of the extracellular matrix through the induction of MMP-2 secretion by satellite muscle cells⁴⁴. Adiponectin is also secreted in an autocrine fashion by skeletal muscle tissue, and the inflamed environment stimulates the muscle production of gAd⁴⁴. In this context, the importance of adiponectin is further underlined by the evidence that decreased plasma adiponectin is associated with reduced regenerative potential of skeletal muscle⁴⁴.

Studies on mice have also demonstrated that leptin affects muscle tissue by increasing skeletal muscle mass and altering its miRNA expression⁸⁰. Similarly, Il-6, an adipo-myokine that is secreted both by adipose and muscle tissue has been shown to stimulate satellite cell activation and muscle repair at the muscle level⁸¹. It has also been recently discovered that a novel adipokine, CTRP3, is involved in the proliferation and differentiation of myoblasts. CTRP3 is expressed in muscle cells and acts in an autocrine/paracrine fashion⁸². In addition, other adipokines have also been shown to regulate myogenesis during muscle regeneration⁸².

HUMORAL FACTORS

Soluble factors participate in the signaling process between the immune system, fascial tissue, and muscle tissue. HGF, FGFs, TGF β s, MSTN, IGF, TNF α , PDGF, IL-6, LIF, VEGF, EGF, KGF, are secreted by different cell types, including fibroblasts, myofibroblasts, muscle cells and immune cells²¹. Other factors, such as TGF- β 1, are trapped in the ECM via specific binding proteins (decorin and biglycan) and can be released by mechanical triggers^{18 21 83 84}.

In adult skeletal muscle, TGF- β 1 hinders muscle regeneration and promotes muscle atrophy and fibrosis. In particular, TGF- β 1 inhibits satellite cell proliferation, myofiber fusion, the activation of muscle-specific genes and, after injury, induces myoblast to myofibroblast conversion⁸⁵⁻⁸⁷. Furthermore, neutralization of TGF- β 1 reduces scar tissue formation and improves muscle tissue healing⁶².

IMMUNE CELLS AND INFLAMMATION

The regenerative process in skeletal muscle also requires the participation of non-satellite cells, such as perivascular and immune cells (Fig. 1)⁸⁸. Inflammatory cytokines (IFN-g and TNF), released at the site of injury, induce the polarization of infiltrated monocytes to M1

macrophages (classically proinflammatory). These cells, in turn, release other inflammatory cytokines and IGF-1, which activate muscle satellite cells^{89 90}. Later, changes in the biochemical environment (cytokines) at the site of injury, induce the polarization of M1 macrophages to M2 anti-inflammatory phenotype. M2 macrophages inhibit inflammation by secreting IL-4, IL-10, TGF- β 1, and support myogenesis by secreting IGF-1⁹⁰. M2 macrophages also induce angiogenesis and promote extracellular matrix remodeling⁹⁰⁻⁹². The role of monocytes in the regeneration process of skeletal muscle has been demonstrated in mouse models, where a reduction of monocytes in the bloodstream or skeletal muscle has been shown to impair the regenerative potential of muscle^{93 94}. In a mouse model of muscular dystrophy, suppression of proinflammatory macrophage activity by IL-10 reduces the severity of the disease⁸⁹. This switch from M1 inflammatory to M2 anti-inflammatory and pro-regenerative macrophages is critical for an effective regeneration of the skeletal muscle⁹⁴⁻⁹⁶. In the early phases following muscle injury, inflammation favors muscle regeneration by inhibiting satellite cell death and promoting myoblast proliferation⁴⁴. In the later phases, in contrast, Treg cells enhance the regenerative potential of skeletal muscle by protecting injured tissue from inflammatory damage, promoting satellite cells differentiation (by amphiregulin), and inhibiting fibrosis^{97 98}. During chronic inflammation, such as those occurring in muscular dystrophies, the ECM accumulates and replaces muscle tissue with fibrotic tissue⁶⁷. During muscle regeneration, anti-inflammatory macrophages induce fusion, growth, and differentiation of muscle cells by TGF- β , low levels of TNF- α and IGF-1^{99 100}.

The dense network of the ECM acts as a physical barrier against the movements of cells. Therefore it must be weakened by fragmentation to allow cells to penetrate it. The binding of integrins with laminins and type IV collagen on the basal lamina prevents neutrophils from reaching the skeletal muscle¹⁴. In the area of damage, different cells, such as fibroblasts, macrophages, endothelial cells release several proteases that fragment the ECM¹⁴. The ECM also has a positive role for cell invasion into the injury site. Fibronectin, type IV collagen, laminin, entactin and proteolytic fragments of fibronectin and laminin, all act as guides and chemoattractants for immune cells and myoblasts^{14 101}.

Interestingly, in aged organisms, the mass and strength of skeletal muscle are reduced, and satellite cells have impaired regenerative potential. Although the myogenic commitment of satellite cells is not affected by aging, their capacity to self-renew is reduced¹⁰². Emerging evidence suggests that changes occurring in the satellite cell niche contribute to the reduced regenerative potential of aged muscle.

MECHANICAL STRESS

Mechanical stress has a reciprocal influence on muscle and ECM. The ECM influences muscle cell alignment and activity, and muscle activity influences collagen fiber alignment²⁶. It is well known that physical exercise is healthy for the organism, but only recently has it been appreciated that mechanical loading of skeletal muscle post-injury also triggers many beneficial responses that enhance skeletal muscle regeneration and reduce fibrosis (Fig. 1)¹⁰³⁻¹⁰⁷. Skeletal muscle loading can directly increase skeletal muscle regeneration by stimulating the activation of SCs, attracting exogenous myogenic stem cells and stimulating angiogenesis^{106 107}. Moreover, mechanical loading of newly formed muscle fibers is crucial for maturation of the tissue and of the myotendinous junctions. Interestingly, mechanical stimulation, in the form of stretch activation, massage therapy, and physical manipulation can improve healing of muscle tissue after damage, exerting anti-inflammatory and anti-fibrotic effects¹⁰⁸⁻¹¹⁰.

The formation of scar tissue, secondary to an injury or pathogenic process, modifies the biomechanical properties of the connective tissue. It also leads to a reduction in gliding between adjacent tissues⁶³. Several studies have shown that physical exercise in Duchenne muscle dystrophy and skeletal muscle-injured mice can prevent fibrosis and enhance muscle performance¹¹¹⁻¹¹⁴. Parenthetically, removal of stress, via mechanical unloading, has been shown to reduce muscle regeneration after injury¹¹⁵⁻¹¹⁷. After this initial resting phase, however, the absence of mechanical loading reduces the extent of muscle regeneration⁷³. As demonstrated in ovariectomized mice, mechanical stimulation of muscle fibers can inhibit fat accumulation in skeletal muscle tissue, a side effect of ovariectomy⁶⁶. Mechanical stimulation has also been proved to prevent satellite cells differentiation toward an adipogenic fate⁶⁶.

The contractile activity of muscle cells stimulates the production of myokines, such as IL-6¹⁰⁷. Transient and short-term exercise-induced production of IL-6 is beneficial for muscle metabolism, however, long-term IL-6 production is detrimental and is associated with muscle atrophy¹¹⁸.

Myokines are proteins secreted from skeletal muscle cells that exert autocrine and endocrine effects and allow communication with adipose tissue, liver, and pancreatic cells¹⁰⁷.

Mechanical stress is known to influence the structure the ECM. Deposition and alignment of the collagen fibers secreted into the extracellular space (to form the ECM matrix) is driven by the position and the orientation of the connective fibroblast-like cells²⁶. At molecular

level, the alignment of intracellular actin fibers in collagen-producing cells guides the parallel deposition of extracellular collagen²⁶. Therefore, the stress produced by cytoskeletal proteins of cells can influence the structure of ECM¹⁸.

Mechanical load also influences fiber alignment by acting on ECM protein synthesis and degradation²⁶. Strain-stabilization, a mechanism relating mechanical stress and collagen fiber orientation, involves mechanical activation of enzymatic degradation of the collagen fibers²⁶. ECM fiber orientation, in turn, affects cell activity, differentiation, and migration^{119 120}. Mechanical stress, in the form of traction, also stimulates the regeneration of deep fascia in animals subjected to leg lengthening^{28 121}. Shear stress applied to the tissue can also modify the alignment of collagen fibers²⁶.

The sensitivity of tissues to mechanical stress is dependent on the presence of TGF- β 1 in traction-sensitive protein complexes that can activate/deactivate TGF- β 1 in response to contractile force changes⁸³. These mechanical stresses can originate in the extracellular environment (injury) or by cell contraction (myofibroblasts or muscle cells)⁸³. The mechanical communication between extracellular and intracellular environments is due to specific cell-ECM and cell-cell interactions mediated by protein complexes¹²². Among these, integrins function as mechanotransducers that can transmit tension in the ECM to the cell and activate cellular responses¹⁸. Cells can sense changes in ECM stiffness and mechanical stress by cytoskeletal actomyosin contraction via integrin¹²². Proteins of the ECM interact with cells by integrins, assembled with other proteins in supramolecular adhesion complexes. The extracellular mechanical stress is transduced into intracellular events, by specific integrin-actin cytoskeleton interactions. Mechanical stimuli can alter the membrane assembly of these adhesion complexes and activate specific signaling processes, such as RhoA-induced actin stress fiber formation¹²³⁻¹²⁷.

The input signals for the remodeling of the ECM are transmitted by ECM receptors, such as integrins, laminin receptors, syndecans, and proteases, including MMPs, serine protease (e.g. plasmin, plasminogen activator and uPAR) and cysteine protease (e.g. cathepsins) families and by structural tension provided by cells and extracellular proteins¹⁸.

In the integer tissue, there is always a tensional homeostasis between cell traction and ECM stiffness¹²². There are distinct intracellular protein complexes, such as SPARC-ILK and Rho-A, that can also provide the tension required for FN assembly at the cell surface¹⁸. Moreover, FN can also induce cell contraction¹⁸.

NERVOUS TISSUE

Reinnervation of injured skeletal muscle is crucial for effective and complete regeneration of the tissue (Fig. 1)¹⁴. In particular, the formation of neuromuscular junctions (NMJs) drives gene expression in the regenerating myotubes^{128 129}. The complex ECM network acts as tissue stabilizer and guides the formation of new NMJs¹³⁰. Therefore, ECM is essential for reinnervation of injured skeletal muscle¹⁸. Somewhat surprisingly, however, the presence of nerves does not appear to be critical in the initial phases of muscle regeneration¹⁴. After muscle injury, the regeneration process restores muscle tissue, ECM, nerves, and their connections. Due to specific proteins, such as agrin and s-laminin and components of the basal lamina (BL), skeletal muscle retains the memory of the original NMJ sites and can guide the formation and differentiation of new NMJs at same location as in pre-injured muscle^{14 131}. Integrity of the BL surrounding muscle fibers and motor axons, however, is crucial for successful re-innervation and regeneration of muscle tissue¹⁴. The BL surrounding the nerve can act as a scaffold and a guide axon regeneration toward the original NMJ site. When the continuity of the BL is disrupted, re-innervation of the regenerating muscle is less efficient¹⁴. Nevertheless, even in the situation of BL disruption, NMJs can readily form at the original NMJ sites when contacted by a growing axon¹⁴.

CONCLUSIONS

Regeneration is the evolutionary key to preserve tissue function during aging and after injury. In humans, different tissues and organs have different regenerative potentials. However, tissues with substantial regenerative capacity can fail to regenerate because of disease or antagonistic physical and biochemical factors. Skeletal muscle and fascial tissues have a remarkable ability to regenerate. Nevertheless, their regeneration is strongly dependent on their close interaction and the presence of nervous and adipose tissues. Moreover, the regeneration process can be easily hindered in favor of non-functional fibrotic tissue accumulation. This, in turn, results in loss of the original mechanical and biological function of the injured tissue, increasing the susceptibility to re-injury, and the development of chronic pain^{110 132}. ECM and fibroblasts activity play a fundamental role in the reaction of skeletal muscle to injury¹³³. Regenerative medicine aims to improve recovery and regeneration of damaged tissues. Over the last decade, cell therapy and bio-engineered synthetic scaffolds have been employed to enhance tissue

repair^{18 22 133-136}. These approaches aim to replace damaged tissue with new functional tissue by supplying ECM-like structures with active cells¹⁸.

Although the results of regenerative medicine trials are still not sufficiently encouraging, a deeper comprehension of the complex mechanisms underlying tissue regeneration can significantly improve the outcome of future clinical studies.

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Mechanical bowel obstruction secondary to fecal impaction with superimposed Ogilvie Syndrome

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Ogilvie's syndrome is a disorder characterized by massive dilation of the colon in the absence of mechanical obstruction. Fecal impaction is typically a disorder of the elderly and results largely from the inability to sense and respond to the presence of stool in the rectum. Both conditions can present with abdominal distension and pain and both can result in colon damage if not decompressed.

A 67 year old male with a past medical history of cerebrovascular accident with left-sided residual weakness presented with abdominal distension, pain and concurrent urosepsis. Abdominal imaging revealed massive colonic dilation superimposed on a fecal impaction. Multiple attempts at mechanical disimpaction and the use of neostigmine returned the stool pattern to normal.

Multiple comorbidities in elderly patients may result in both a delay in recognition and an overlap of disease processes.

Key words: Fecal impaction, Ogilvie Syndrome, urosepsis, Colonic ileus

INTRODUCTION

Ogilvie syndrome is also known as acute colonic pseudo-obstruction (ACPO), or acute colonic ileus. It is characterized by massive dilation of the bowel in the absence of a mechanical obstruction. The precise etiology of ACPO is not known but the risk factors suggest that an antecedent severe illness is a finding. In fact, in a review by Vanek ¹ only 5.5% of patients presented without a known associated cause. The most common predisposing conditions were infection, nonoperative trauma, and cardiac disease. The diagnosis requires abdominal imaging which will both rule out structural obstruction and confirm proximal colonic distension. Implementing a management is urgent. Colonic distension can result in ischemia and perforation resulting in a mortality rate which is approximately 15 percent with early appropriate management, compared with 36 to 44 percent in perforated or ischemic bowel ¹.

Fecal impaction is a consequence of constipation and can present with clinical characteristics of ACPO including distension and pain. The diagnosis and treatment include digital rectal exam, imaging and bowel disimpaction by removing the structural obstruction from the rectum. The differential diagnosis includes multiple conditions such as functional disorders, intrinsic colon disease, medications and neuromuscular disorders. We present a 67 year old male with a fecal impaction who developed clinical characteristics of ACPO after becoming septic with a catheter-associated urinary tract infection.

CASE

A 67-year-old man with a past medical history of cerebrovascular accident with left-sided residual weakness presented to the Emergency Department with

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confusion after a mechanical slip and fall. He had a history of home catheter use for voiding assistance but denied constipation or emesis. On admission his abdomen was slightly distended with positive bowel sounds and his temperature was 38.8 C. Laboratory studies included mild hyponatremia 133 mmol/L, elevated blood urea nitrogen 27 mg/dL and elevated creatinine 1.63 mg/dL, consistent with mild acute kidney injury. Liver function tests, including serum aminotransferases, alkaline phosphatase, bilirubin, and amylase were all within normal limits. His white blood cell count was 22,000. Both urine and blood cultures revealed *Providencia stuartii*, susceptible to third-generation cephalosporins. An upright KUB (Fig. 1) revealed an ileus pattern superimposed on fecal impaction, and a CT without contrast (Fig. 2) revealed a very large fecal impaction distending the rectum with considerable fecal matter and gas behind the impaction throughout the colon and modest distal small bowel stasis. No evidence of mechanical obstruction was visualized other than the impaction but colonic diameter was 11 cm. He was given intravenous antibiotics and nasogastric tube placed. The patient underwent numerous bedside manual disimpactions, enemas, and castor oil without significant improvement. The clinical picture was complicated with persistent abdominal discomfort with any oral intake, inadequate stool output, poor abdominal physical exams, and follow up abdominal XRays worrisome for colonic ileus. When these measures did

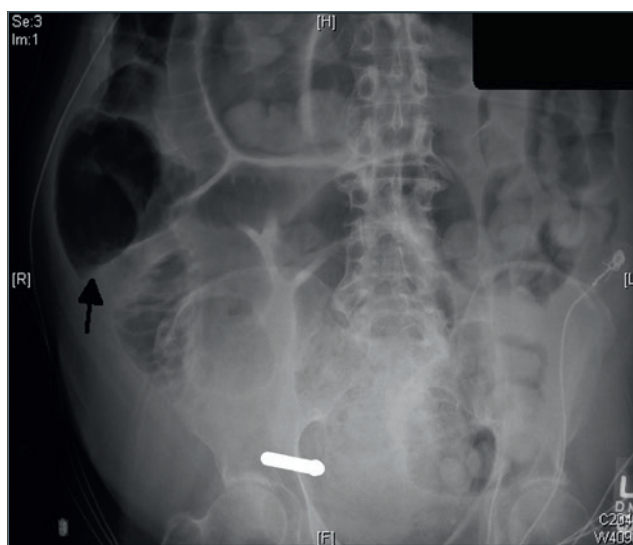


Figure 1. KUB. There is a moderate amount of gas and a large amount of fecal matter throughout the colon. Large fecal bolus is seen in the rectum secondary to impaction (white arrow). There is some small bowel gas accumulation. Ileus pattern superimposed on fecal impaction would have this appearance. Gas in right hemicolon (black arrow).



Figure 2. CT abdomen and pelvis. There is a very large fecal impaction distending the rectum (white arrows). There is considerable fecal matter and gas behind this impaction throughout the colon. There is modest distal small bowel stasis that may be causing partial obstruction of the colon.

not result in meaningful clinical improvement, decompressive colonoscopy was scheduled. However, due to a newly-positive *Clostridium Difficile* Toxin B Gene by polymerase chain reaction test the procedure was delayed. Infectious colitis was not felt to be a precipitating factor, given its timeline later in the hospital course. Treatment for the infection was initiated, at which point the Gastroenterology consult service recommended neostigmine for concern of possible pseudo-obstruction (Ogilvie Syndrome). Constipation and abdominal distention did not improve. Flexible sigmoidoscopy and colonoscopy were eventually attempted but were unsuccessful in removing the impaction. The patient developed overflow incontinence diarrhea and ultimately a manual disimpaction under anesthesia was successful. He developed postoperative fever and was found to have positive blood cultures for *Acinetobacter baumannii* complex. After successful parenteral antibiotic treatment he was discharged to a skilled nursing facility.

DISCUSSION

This case is unique because of the clinical findings and X-Rays suggesting Ogilvie Syndrome in a case of

clear mechanical colonic obstruction secondary to fecal impaction. The abdominal distension, gas pattern on X-Ray^{2,3} and pain are common findings to both disorders and in all likelihood there was a component of both disorders in this patient. Most cases of Ogilvie Syndrome have defined antecedent serious illness¹ and this patient presented with urosepsis. His gas pattern on the abdominal X-Ray flat plate was consistent with a colonic ileus that was clearly right-sided. One element, however that was not consistent with Ogilvie Syndrome was the failed treatment with neostigmine. This pharmacologic approach along with resolving any antecedent underlying illness is typically 90% successful in the treatment of Ogilvie Syndrome⁴. One possible explanation for the failure of neostigmine is the structural obstruction of the fecal mass. Nonetheless, colonic obstruction secondary to fecal impaction was our principal diagnosis with superimposed secondary Ogilvie Syndrome added during the management phase. Constipation and abdominal distention are nonspecific symptoms of fecal impaction⁵. Impaction results when the sensory system cannot alert the individual to a slowly increasing burden of stool in the rectum. This translates to stagnant stool collecting in the vault, impairing passage of newly formed stool. Digital (finger) disimpactions serve as first-line therapy, however warm-water and mineral oil retention enemas may be instituted to facilitate passage of hardened stool. Our patient did not respond to any of these initial therapies. Other forms of therapy include local anesthesia to relax muscles surrounding the anal canal thereby providing a larger lumen diameter for passage of stool, and can be effective when used in conjunction with abdominal massage⁶. If all methods prove to be ineffective, decompressive colonoscopy may be used to fragment and eradicate rock-like stool. Both conditions require

urgent medical attention since both can result in bowel ischemia and subsequent perforation.

In summary, a patient with a fecal impaction resulted in mechanical bowel obstruction. He presented with urosepsis and evidence of colonic ileus. His serious systemic illness probably resulted in a superimposed Ogilvie syndrome which would explain the gas pattern on X-Ray and possibly a component of failed treatment with laxatives. The symptoms of Ogilvie Syndrome mimic those of mechanical obstruction of the colon, but no such physical obstruction is present. Nausea, vomiting, abdominal bloating or swelling and constipation are usually present in a patient with a previous serious illness. The diagnosis is established by abdominal imaging⁷.

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Clinical skills are not necessarily impaired, but rather may be improved by ageing

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Introduction. A clinician is an observer of nature, of a biased nature, an observer that cannot use Aristotle's induction method, even as reviewed by Bertrand Russell, but rather the deduction method, as outlined by Albert Einstein and developed philosophically by Karl Popper, Pierre Duhem and by Augusto Murri – Popper's ancient forerunner. One might also mention Antonio Cardarelli – a very intuitive clinician – a follower of Bertrand Russell and of the induction method. The ability to advance hypotheses may even be strengthened in time and as a practical experience enhanced upon ageing.

Successful old age and teaching. A clinician experiencing a successful old age is a wealth that should not be wasted in practice nor, perhaps, in teaching. The advantage of a well-preserved old man, also vs a clinician still far from his sixties, is then in the number of stories and, with respect to clinical semeiotics, in the skilfulness of the examination derived from long-term practice. The problem of the old man, besides losing his neurons, is the capacity of the cognitive reserve based on what Ernesto Lugaro – professor of nervous and mental disease clinics in Turin in the past century – called “neurotropism of the functioning neurons”, i.e. the tendency of neurons to form synapses. The challenge of learning the Information Technology language, grows with ageing and lastly, an old individual enjoys the well-known pleasure of paper communication.

Old clinicians and the general intelligence. A well-aged old clinician retains all the general intelligence developed in his or her youth, and continues to make the best use of it to set and solve problems.

Teaching clinics: true clinics, if not experienced as a practitioner, cannot be taught, nor preserved as a perennial intellectual asset of a well-aged old person (or well-made old person) echoing *La tête bien faite* by Edgar Morin.

Making a diagnosis. The problem here is still the warning of the clinician, of each one of us, that making a diagnosis means knowing a fragment of the real world of which we are part, and that knowing is only possible through a method. A well-made old person knows all this and must teach it through practice, which is also made of tiny observations that are not mentioned in treatises, but should be handed down verbally before they are lost. As Leonardo Bianchi noted in his last academic lecture on old age “we were and are excited about youth, it stimulated often my thoughts, it brightened up my existence year after year with spring fruits”.

Key words: Induction method, Deduction method, Successful ageing, Teaching, True clinics, Making a diagnosis, Skilfulness

INTRODUCTION

You should hardly be surprised that a clinician, a clinical neurologist like myself, who is supposed to explain how the diagnostic and treatment skills do not lose momentum throughout a lifetime, may open his remarks

quoting Albert Einstein (1879-1955): “*without a theory it would be impossible to extract significant information from the background noise of the countless data recorded in nature*”. This statement conveys two main features of a clinician's work – albeit without mentioning them: 1. the need to have a theory, i.e. a prior knowledge

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every time a problem is encountered (the problem will be identified with the patient, since no patient can be seen other than as a problem); 2. the need to draw significant data from the background noise of the story. A clinician is an observer of nature, of a biased nature, an observer that cannot use Aristotle's induction method, even if reviewed by Bertrand Russell (1872-1970), but rather the deduction method, which is inferred in the above quote of Albert Einstein and was developed philosophically by Karl Popper (1902-1994) and Pierre Duhem (1861-1916). You see, clinicians are often seen as the *Cyrenians of science*, a judgement that can only be shared if referred to non-clinical clinicians, i.e. the prescribers of instrumental examinations with which they do not aim at refuting one or more hypotheses originating

from the story. I mentioned Karl Popper, but the philosophy of knowledge by conjectures and refutations has an ancient forerunner – Augusto Murri (1842-1932), who was a professor of internal medicine in Bologna for many years. I would like to report an abstract from one of his lectures, held in 1906¹, which explains the clinician's work: *"before we can start speaking about today's case, let me explain my thought. Today we are not facing a patient, but rather a dead body; what would prevent us from opening it and making a few comments following necropsy? Nothing at all, but this is not clinics. Nor does it look like clinics to introduce a patient, state his or her condition, and highlight the symptoms. True clinics consists in training the mind to explore the pathways that lead to judge the disease. I therefore announce that, once we have opened the body on which we are going to focus today, everything may look plain: the pathologist may not find anything to learn. But things are different for us: now we have to predict whether this is going to be the case. If you only have to see, you may think this is one of the most obvious facts, but things are much different for those that need to foresee"*.

As you may easily understand, foreseeing means acting according to conjectures and refuting them. This is what Murri referred to as the *"elimination method"*, which was a bright preview of Karl Popper and his philosophy of knowledge.

Please keep in mind this methodological introduction, the knowledge and practical application of which can be expanded in time and never decline, provided that old age is a successful old age, the old age to which Stefano Cappa will refer in his lecture, linking cognitive reserve with a successful old age.

Before focusing on the specific theme I first referred to, there is a commonplace you may have often heard, on which I wish to dwell for a moment. People say, *"he was a very intuitive clinician"* when referring, in particular, to

figures that had a strong influence on the history of clinical medicine. Among them Antonio Cardarelli (1831-1927), who was a professor of internal medicine in Naples; while he refrained – in his lectures – from issuing any provisions on the method he implicitly used; he was indeed a follower, as we would say today, of Bertrand Russell and of the induction method.

WHAT IS INTUITION?

What is a clinician's intuition or, more generally, intuition? And how does it develop in time? It turns out from reading Plotinus (203/4-270) or Thomas Aquinas (1225-1274) that *"intuition is the immediate and total act by which God acknowledges the world"*: for me, as a clinician, it is an abstract definition and, as such, irrelevant. At a lower level, I will quote Pietro Greco, director of the Master in Science Communication at Scuola Internazionale di Studi Avanzati in Trieste: *"today we can define intuition as a creative act... that each of us performs when grasping some logical and/or scientific truth without passing through its formal demonstration"*. But this is the point: the formal demonstration. I think that what we call intuition is different in one respect from the rules of classical rationality that provide for any logical and scientific truth to pass through a formal, methodologically codified demonstration: such difference is in the speed with which the mental action is performed by the clinician. If this is the case and *si parva licet comparare magnis*, a clinician, whether young or old, cannot move away from Galileo (1564-1642) and then from Karl Popper and put the hypothesis or, according to Galileo, the assumption at the basis of his work.

THE ABILITY TO FORM HYPOTHESES AND A SUCCESSFUL OLD AGE

But does the ability to form hypotheses decline even in a successful old age, or does it remain unaffected or may even be strengthened in time and as practical experience is enhanced upon ageing? As mentioned, hypotheses originate from the story, from which the background noise should be removed to grasp the meanings, i.e. the hypotheses that need to be refuted. Claude Bernard (1813-1878), a French physiologist, defined the hypothesis as *"the advanced interpretation of natural phenomena"*, quoting John Locke (1632-1704), who defined the hypothesis as the *"assumed cause of an observed phenomenon"*. As you can see, what is new is always partly old.

I think that, at this point of the lecture you have been listening to, an answer can be given to certain questions

on a clinician's maturation throughout his lifetime: 1. Who is going to be richer in terms of prior knowledge, not just of the knowledge acquired in time from a growing number of readings, but also of the knowledge that true clinicians can only acquire on the field – a young or an older individual in a successful old age? 2. Who is more skilled at extracting meanings from the background noise of sometimes confusing stories – a young or a well-aged individual? Augusto Murri used to admonish students that *"there is no story without lies"*, an admonition that is often perceived as a sign of an ageing clinician's mandatory wisdom. True, in time you listen to stories you have heard before, but unheard stories will surely come even if you are eighty or beyond.

SUCCESSFUL OLD AGE AND TEACHING

In the light of the above, a clinician experiencing a successful old age is a wealth that should not be wasted in practice nor, perhaps, in teaching: Antonio Cardarelli, born in 1831, was still lecturing in 1923. But if you continue to follow me in the recollection of the clinical method, you will also find other reasons not to reject, and possibly favour, an old clinician. I told you that a clinician works by conjectures and refutations, and that conjectures originate from the stories, but the first refutation can also consist in asking questions aimed at demolishing the first conjecture; clinical semeiotics and, ultimately, instrumental investigations, will only come later. The advantage of a well-preserved old man, also vs. a clinician still far from his sixties, is then in the number of stories and, with respect to clinical semeiotics, in the skilfulness of the examination derived from long-term practice. The problem of the old man, besides losing his neurons, is the capacity of the cognitive reserve based on what Ernesto Lugaro (1870-1940), professor of Nervous and Mental disease clinics in Turin in the past century, called *"neurotropism of the functioning neurons"*, i.e. the tendency of neurons to form synapses.

The theme of prior knowledge, or the bulk of knowledge that allows, after listening to a story, to make conjectures to be refuted, is critical as related to ageing, as much as preserving the primacy of imagination and fantasy, which are both measures of general intelligence. There is field learning, developed through operational practice, that requires, like any learning, the filter of meanings, but there is also an inevitable compulsory, lifelong learning that is the knowledge of the codified results of research in the specific subject, neurology for me, as well as on the subjects that fuel neurology, or are fuelled thereby. If the brain is well preserved, field experience and the resulting knowledge

will merge into what Zulch (1910-1988) referred to in 1969 as a *"peculiar mixture of doctoring and a very high intellectual demand"*. There is, however, a more recent issue concerning ageing individuals, namely information technology communication (IT). While the IT language is not precluded to anyone, it has two limits: on one hand the boundless and unfiltered dissemination of data, but here again we face the issue of the meanings to be extracted from the background noise; on the other, the challenge of learning the IT language, which grows with ageing, perhaps even after 25 years of age. Lastly, an old individual enjoys the well-known pleasure of paper communication. Benedetto Croce (1866-1952) used to talk about the pleasure of touching and smelling the paper of a newly printed book, but I am not sure that bibliophiles are still so common. Certainly, most people in their eighties or older are too familiar with paper-based communication to accept video information without feeling disturbed by it: what counts is to acquire knowledge one way or another, and a successful old individual cannot and should not fail here.

THE VALUE OF THE COGNITIVE RESERVE

I have been writing so far about a small or large cognitive reserve as a prerequisite for a successful old age and for the subsequent functional potentials. But a cognitive reserve needs a base endowment, which is not the same for everyone. Therefore, I will try to answer the following question: can everyone become a clinical neurologist and then grow, and finally be preserved in time? I will answer by reverting to the above quote of Zulch: neurology calls for *"a very peculiar mixture of doctoring and high intellectual demand"*. If this is true, not everyone can become a clinical neurologist, but some or many can be educated for the purpose, if they satisfy the condition by which Percival Bailey (1892-1973) acknowledged the right to neurology to those whose main interest was *"to dream and think about the nervous system"*. The next step is the education of young people preparing for their future old age. Herbert Simon (1916-2001) wrote that the human mind is a mechanism devoted to *"general problem setting and solving"*. Other than most people believe, the development of general intelligence is what allows to develop specialized skills; if it is true that the more relevant is general intelligence, the greater is the ability to set and solve special problems, the consequence is that education should indeed promote the development of general intelligence. Some of you may call me an academic wanderer, but I am not. The development of general intelligence raises the doubt that allows – according to Juan De Mairena (1865-1909) – to *"rethink what is*

thought", to doubt about one's doubt: according to the oldest philosophy, it implies the *ars cogitandi* (as deduction/ induction), the art of arguing and discussing.

PROMOTING THE DEVELOPMENT OF GENERAL INTELLIGENCE

Promoting the development of general intelligence can be a goal of any teaching, but most of all of clinical teaching; this should demonstrate the intrinsic complexity of clinics: it brings back to the mind Euripides (465 b.C.-408 b.C.) who wrote, in *Medea*: "*the gods give us many a surprise: the expected does not happen and a god opens the door to the unexpected*". Luckily the gods tend not to interfere with clinical neurologists, but we should not forget that the unexpected can, indeed, happen. I believe that none of you fails to understand that a well-aged old clinician retains all the general intelligence developed in his or her youth, and continues to make the best use of it to set and solve problems.

WHAT IS CLINICAL NEUROLOGY?

What is, then, the clinical neurology that I used as an example for any clinics? A clinician's goal is to reproduce a paradigm, from the symptom to aetiology aimed at identifying the cause as re-identification or as identification *ex novo* by the clinical researcher, who is the same practitioner exploring the unknown beyond a poorly defined limit. What I see here is the research as an intrinsic vocation of man's nature: the knowledge of the truth, i.e. of the cause for natural events, of which illness is, as mentioned, a biased variation. But research can only survive if it connects the past with the future, and the past is in the memory of old people, including great ones, who can be somewhat hesitant with respect to short-term memory but not to long-term memory, which they fondly cherish – if they are successful old people. According to Edgar Morin's (1921) idea of unique cultures, I am reiterating Croce's intuition of the future as a development of the past, i.e. of the historical nature of the present.

A LIST OF THE DISCUSSED TOPICS AND A PERSONAL STORY

In the first part of this editorial I discussed about intuition and classical rationality as a theoretical base for knowledge. In the second part I reintroduced the elimination (deduction) method according to Popper's philosophy of knowledge, which I described with reference

to clinical neurology. In the third part I wandered on the general intelligence which can grow by teaching and learning complex clinical topics, including, of course, clinical neurology, of which I have been professor, after a competition in 1971. With this note I introduce you to the final part of my *divertissement*. I always spoke as a clinical neurologist, but at the 1971 competition I was judged capable to act as a clinician for nervous and mental diseases. With this personal, yet generally meaningful story, I wish to tell you how a clinician that looked at neurological, rather than at psychiatric diseases has changed in time, particularly after closing his academic career in 2008 and finding renewed interest in psychiatry. In 1975 the few (21) full professors of the time, including myself, were invited to choose between neurology and psychiatry for their future academic career; we all went for neurology without hesitation, in that to us it was the noblest part, in scientific terms, of nervous and mental disease clinics, compared to phenomenological and descriptive psychiatry, albeit already headed towards great drug therapy. But we looked at psychopharmacology as neuropsychopharmacology and at a part of psychiatry – biological psychiatry – as neurology investigating the neurobiological basis of mental disorders. And then we were confident that our clinical skills developed in the unitary context of neuropsychiatry would not be lost, and they were not. In the following years scientific psychiatry was more and more often recognized as biological psychiatry, and thus returned to neurobiology, a mandatory part of neurology and psychiatry. What I told you is not my story but a general story, albeit personal at a first glance, that I experienced in my youth, as well as in my mature and old age. But what happened for me as a clinical neuropsychiatrist after 1975, i.e. after I was academically redefined as a clinical neurologist? It happened that in time (and I think other people of the same age share the same experience) I developed the ability to: 1. follow Michael Balint's (1896-1970): "*physicians should give themselves*"; 2. look at the patient as an individual, "*without using or misusing* (as wrote Cesare Frugoni (1881-1978) in his *Ricordi e Incontri* ², (published in 1974) *pretentious words like mission, priesthood, sacrifice – words that are repeated time and again to us, often unduly*". I like to quote Frugoni, who was a professor of internal medicine in Rome and wrote, on the last page of the referenced book, "*despite progress, medical practice will always be fraught with challenges and responsibilities, but the medical spirit will not change to the orders of an invisible and powerful chief – duty*". Well, an old man that had this invisible and powerful chief in his youth will be more respectful of duty due to the very introjection thereof experienced in his past. Perhaps Walt Whitman (1819-1892) went too

far when he wrote in his *Youth, Day, Old Age and Night*: “youth, you are all about grace, vigour, appeal, but are you aware that old age can follow you with the same grace, appeal, and vigour?”, but this statement is very comforting to all of us.

But now let me come to my conclusion, in the absence of Edgar Morin, on the uniqueness of cultures with reference to the clinics to be taught and experienced as a practitioner. Because true clinics, if not experienced as a practitioner, cannot be taught, nor preserved as a perennial intellectual asset of a well-aged old person (or well-made old person) echoing *La tete bien fait* by Edgar Morin.

THE LINK IS IN THE METHOD

The link is in the method, and this is why we can say that, while a clinician’s practical experience cannot exclude a method – the method – the clinician participates in turn in Morin’s utopia non-utopia with respect to the uniqueness of cultures.

Reference here is made to the philosophy of knowledge, which drives the reconstruction of the archetype or diagnostic paradigm, with a very strong link between humanistic culture and scientific culture. Galileo Galilei was a great scientist because he observed the earth’s movement around the sun but also, and perhaps most of all, because he designed a scientific knowledge

method that can be applied to non-scientific knowledge. The problem here is still the warning of the clinician, of each one of us, that making a diagnosis means knowing a fragment of the real world of which we are part, and that knowing is only possible through a method. A well-made old person knows all this and must teach it through practice, which is also made of tiny observations that are not mentioned in treatises, but should be handed down verbally before they are lost. As Leonardo Bianchi (1848-1927) noted in his last academic lecture on old age³: “we were and are excited about youth, it stimulated often my thoughts, it brightened up my existence year after year with spring fruits”. Claiming he had been educated through Seneca’s philosophy, Leonardo Bianchi could not write anything different, nor could anyone who looks at old age and death as functions of the species required to ensure the continuity of life.

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REVIEW

The mirror neurons

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Origins. The mirror neurons (MN) have been described for the first time more than 20 years¹⁻³ ago in the macaque's ventral premotor area F5 and in the inferior parietal lobule (IPL).

Properties. These areas have unexpected properties (a) to code the objectives of motor acts; b) to respond to the presentation of object (area F5); c) to code the peripersonal space (area F4). In a simplistic and schematic way, the MN circuit is made up by neurons of the superior temporal sulcus (STS) that fire during the observation of others' motor acts and project to the IPL, connected to the ventral premotor cortex.

Outcomes. The mirror system (MS), therefore, seems to be both innate and acquired and though it is plastic. Behavioral and neuropsychological studies suggested that the simple observation of motor acts facilitates the motor memory and the motor performance both in healthy people and in stroke patients. In the post-stroke physiotherapy.

Conclusions. The mirror mechanism allows the understanding of actions or emotions that put its roots in the same ability to act or feeling emotions.

Key words: Mirror neurons, Space-sensitive MN, View dependent MN, MN sensitive to the value of an observed action, Space-sensitive MN

MIRROR NEURONS

In details, in F5, beside pure motor neurons, there are two categories of *visuomotor* neurons:

- "canonical neurons" (responsive to the presentation of tridimensional objects);
- MN (responsive to the observation of motor acts).

The demonstration of MN had meaningful consequences in the understanding of brain functions and of the aging variability of the different neuronal systems thus allowing a better understanding of senescence variability.

MN fire either when the macaque performs a motor act or when it observes the motor act executed by someone else.

MN are involved in the understanding and in the imitation of other's motor acts; moreover, they constitute the neuronal basis of empathy and the first modalities of social interaction such as language.

In humans, besides the parietal-frontal circuit, MN have also been described in the hippocampus, insula and cingulate cortex.

In a simplistic and schematic way, the MN circuit is made up by neurons of the superior temporal sulcus (STS) that fire during the observation of others' motor acts and project to the IPL, connected to the ventral premotor cortex.

The main property of MN of F5 is to code the *objectives* of a motor act; experiments on the macaque showed that MN fire either when it grasps food with its hand or when it does it with an inverse pliers when the grasping motor act requires the opposite movement that occurs during the grasping without pliers (with the inverse pliers, grasping an object requires the hand opening); therefore, these neurons fire similarly even with different movements because *the objective of the motor act* (grasping) is recognized and not the simple motor act. Moreover, single neuron extracellular recording allowed

to study neuronal outputs: these latter are the same either when the macaque *executes a motor act* or when it observes a motor act executed by someone else. Therefore, the MN code the motor act either during the *active execution* or during the *observation*

MN have also visual properties, indeed there are:

- *Space-sensitive MN*;
- *View dependent MN*;
- *MN sensitive to the value of an observed action*.

Space-sensitive MN⁴ allow an appropriate behavioral response according to the location in the *peripersonal* (close and thus with the observer possibility of action) or *extrapersonal* space (far and thus with the observer impossibility of action) of an observed action.

View-dependent MN facilitate higher order visual neurons in the *perception of details of observed actions*; indeed, there are three types of MN that fire electively when the stimulus is presented in the subjective, lateral or frontal perspective; other MN instead, fire independently of the perspective of the presentation of visual stimuli.

MN *“sensitive to the value of an observed action”* are located in the orbito-frontal cortex and in the cingulate gyrus; they fire when a large reward is anticipated; these areas, that associate objects to a reward, are fundamental in determining the value-related response of MN. The value attributed to a peculiar object when grasped is fundamental to select an appropriate behavioral response.

Nevertheless, this ability is not only limited to F5, indeed, about half of the pyramidal neurons (PN) of F1 fire when a grasping act is observed; however, comparing the properties of the MN of F1 with those of the MN of F5, the visual response in F1 are much weaker than those in F5. Moreover, 25% of PN show a complete firing suppression during grasping observation while they strongly fire during the grasping execution. It has been suggested that the suppression of these PN may be involved in the inhibition of movements during the observation of actions.

It has been hypothesized that MN allow to differentially code two identical motor acts according to the different context^{5,6}. This ability, based on the context or on a previous experience, would allow to understand other's intentions. However, an observed action, in order to make the MN firing, should belong to the repertoire of that specific species: the act of biting evokes the MN firing either in humans, or in dogs or in monkeys while the barking act evoke the MN firing only in dogs.

The comprehension of actions through the activation of the mirror system (MS) is different from the associative type understanding of actions; indeed, the MS has the capability to understand the pertinence of an action with respect to the aim of the observed movements by comparing them with its own repertoire.

Therefore, the richest the motor repertoire, the greater is the capability to understand others' actions. In other words, our ability to act allows us to immediately attribute a meaning to the observed movements, i.e. to understand them in terms of possible aims. The MS is not the only allowing us to understand others' actions but, probably, it is the most straightforward system that allows people to reciprocally interact. Indeed, it is involved in the imitation process by generating an internal representation of the observed act (potential act) that would render possible to learn by imitation. Moreover, the MS is also involved in emotional processes; indeed, besides the prefrontal MS there is also a limbic MS (insula, mesial anterior frontal cortex) that would be involved in the identification of affective behavior and, though, it would be at the basis of empathy. Recent functional Magnetic Resonance Imaging (fMRI) studies showed how the presentation of faces, with different emotional expression, evoked the activation of the same brain areas that activate during the personal experience of that peculiar emotion (a perceived painful stimulus and the observation of a pain evoked facial expression determine the activation of the same cortical area, the insula).

The limbic MS, in contrast with the prefrontal one, modifies with aging: fMRI studies, indeed, have shown that by observing others' painful stimuli, the activation of anterior insula and of the mesial anterior frontal cortex (anatomical bases of empathy), progressively weakens with age. About the innate or acquired nature of the MS, there are evidences in both directions; for example, smiling to a few hours newborn, will evoke, with high degree of probability, a similar response; on the other hands, fMRI experiments evaluated the activation of the MS of a professional dancer who was taught a specific dance step: at different (progressive) stage of learning corresponded different (increasing) degree of the activation of the MS.

The MS, therefore, seems to be both innate and acquired and though it is plastic. Behavioral and neuropsychological studies suggested that the simple observation of motor acts facilitates the motor memory and the motor performance both in healthy people and in stroke patients. In the latter, neurons responsive to the observation of manual action have been identified in the premotor and supplementary motor cortices, in the inferior frontal gyrus, in the inferior parietal cortex and in the middle temporal gyrus. Based on this observation, some experiments evaluated the effect of a combined approach of neurorehabilitation and motor acts presentation. Actually, in stroke patients the observation of motor acts may facilitate the motor re-learning process through the activation of the MS. Therefore, this combined neuro-rehabilitative approach may be proposed as a new strategy in the post-stroke physiotherapy.

In conclusion, the mirror mechanism allows the understanding of actions or emotions that put its roots in the same ability to act or feeling emotions ⁷.

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Cognitive reserve and successful ageing

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Background. The concept of cognitive reserve was introduced in the neurological field to account for the observation of individual discrepancies between the level of brain pathology and the observed cognitive/functional deficits. The notion of brain reserve provides a strong foundation for the recent increase of interest in modifiable risk factors as a strategy for brain health promotion.

Strategies. There is now evidence of protective effects on cognitive decline and dementia for physical activity, Mediterranean diet, cognitive training and social engagement, which may all be considered as contributing to brain and cognitive reserve mechanisms. Besides controlling risk factors, an area of great interest is the possibility to act positively on the reserve by means of active intervention. This possibility is suggested by the results of several cognitive training studies in healthy elderly subjects.

Conclusions. Even modest effects on the age of onset or the rate of cognitive decline would have an enormous positive impact on successful aging at the population level worldwide.

Key words: Cognitive reserve, Modifiable risk factors, Cognitive training, Social engagement, Mediterranean diet, Active interventions

The concept of cognitive reserve was introduced in the neurological field to account for the observation of individual discrepancies between the level of brain pathology and the observed cognitive/functional deficits¹. The early observations at the roots of the concept came from neuropathological studies of Alzheimer's disease (AD), in which some individuals were found to demonstrate less cognitive impairment than others affected by a comparable degree of neuropathology². The possibility to assess clinico-anatomical correlations *in vivo* opened new possibilities to the investigation of this intriguing phenomenon. An early study¹, based on the 2-dimensional technique of cerebral blood flow assessment, provided group level evidence for the role of education as a modulator of the brain pathology/clinical expression relation. Three groups of AD patients, with low, intermediate and high education were matched for clinical severity. Severity of hypoperfusion, which can be considered as an index of brain pathology, was

inversely proportional to the level of education. In other words, the same level of clinical severity was associated with a more severe involvement of the brain in the more educated subjects, suggesting that education was providing some protection against cognitive decline. These pioneering observations, confirmed by many additional studies, led to the further development of the reserve concept. A proposed distinction is between a "passive" component of reserve (brain reserve), identified by quantitative indexes, such as brain size, neuronal number, density of synapses, and an "active" component, related to functional compensation and reorganization induced by environmental and lifestyle factors, indexed by education, occupational attainment and intellectual activities³. This is clearly an artificial distinction, given the strict intertwining of the two aspects as indicated by the notion of neuroplasticity, linking specific environmental experiences to brain changes. This is now supported by a large number of human studies, from the

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famous observation of increased hippocampal volume in London taxi drivers⁴, to the short term gray matter associated to learning to juggle⁵.

What is now generally accepted is that reserve can act as a modulator, resulting, in the case of progressive neurodegeneration, in delayed clinical expression, and, therefore, faster decline after reaching the diagnostic threshold. The original results reported by Stern et al.¹ have subsequently been replicated and expanded using positron emission tomography measurements of glucose metabolism⁶. In the latter study, the observations supporting the existence of reserve mechanisms were confirmed in a large sample of AD patients, and extended to the prodementia condition of mild cognitive impairment (MCI). A significant association was found between higher education/occupation and lower regional metabolic rate of glucose in posterior temporoparietal cortex and precuneus, i.e. in areas typically affected in AD, both in demented patients and in MCI subjects, which were later found to progress to AD. The results suggest that education and occupation can be considered as surrogate measures of brain reserve, with an impact both on reducing the severity of dementia and on delaying the clinical expression of the brain pathology. Another interesting finding was subsequently reported, again using PET, but measuring a molecular marker rather than glucose metabolism⁷. The same reserve indicators, i.e. education and occupation, were correlated with acetylcholinesterase activity, measured voxelwise by [11C]-MP4A and positron emission tomography. In this case, a positive correlation was found between education and AChE activity in the hippocampus, bilaterally, and between occupation and AChE activity in the right posterior cingulate gyrus. These regions are part of the memory network, thus suggesting that stimulation of cholinergic neurotransmission may be a contributing factor to brain reserve.

The notion of brain reserve provides a strong foundation for the recent increase of interest in modifiable risk factors as a strategy for brain health promotion. There is now evidence of protective effects on cognitive decline and dementia for physical activity, Mediterranean diet, cognitive training and social engagement⁸, which may all be considered as contributing to brain and cognitive reserve mechanisms. It is worth noting that this does not apply only to age associated cognitive disorders, but to a variety of neurological conditions, such as stroke or multiple sclerosis, where cognitive reserve appears to act as a powerful mediator between pathology and functional performance⁹.

Besides controlling risk factors, an area of great interest is the possibility to act positively on the reserve by means of active intervention. This possibility is suggested by the results of several cognitive training studies in

healthy elderly subjects. While the results of training in AD have largely been disappointing, a large-scale study in elderly subjects found a significant reduction of physiological cognitive decline in subjects engaged in working memory training¹⁰. Particularly remarkable are the results of a similar study¹¹, in which the positive effect of training was not limited to test performance, but extended to functional activities of daily living. The FINGER study in a large sample of at risk subjects, based on a comprehensive intervention on risk factors combined with cognitive training, reported significant effects on several cognitive variables¹². The cognitive changes due to training in a sample of MCI patients were associated with changes in brain activity during a memory task measured with functional magnetic resonance¹³.

The recent observations of a protective effect of bilingualism, resulting in a delayed age at onset of dementia¹⁴ and in milder cognitive effects of stroke¹⁵ has led to the hypothesis that learning a second language may be a privileged cognitive stimulating activity, an interesting concept that needs to be supported by experimental evidence.

Finally, neuromodulation approaches based on transcranial magnetic stimulation or direct current electrical stimulation, which have been shown to provide some performance enhancing effects in AD and MCI¹⁶ may also be considered as a potential tool acting on cognitive reserve.

To summarize, the concept of cognitive/brain reserve is based on solid experimental evidence, and provides a useful theoretical framework for the development of programs aiming at the promotion of brain health in the elderly. While the benefits of such programs may not be apparent at the individual level, even modest effects on the age of onset or the rate of cognitive decline would have an enormous positive impact on successful aging at the population level worldwide.

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REVIEW

Chronic kidney disease and ageing

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In recent decades, life expectancy has significantly extended, and the number of elderly people in each population increases significantly during the subsequent years. Ageing is associated with a physiological deterioration of kidney function, however, in patients with additional diseases such as diabetes, hypertension and obesity, there is often stronger severity of kidney damage. It has been estimated that the prevalence of chronic kidney disease (CKD) in the older population is several times higher than in the general population. It is considered that in addition to the mentioned above comorbid the socio-economic factors also increases prevalence of CKD. The occurrence of CKD significantly increases the mortality, deteriorating the quality of life of these subjects and is also severe financial problem for the health care system because of the high costs of renal replacement therapy. For this reason, renal replacement therapy in elderly patients is expensive and not always brings measurable benefits.

Key words: Chronic kidney disease, Ageing, Renal replacement therapy

INTRODUCTION

In recent decades, life expectancy has significantly increased and it seems that this trend will be maintained, which will result in constantly growing number of elderly people in coming years¹. It has been estimated that in 2030 in the United Kingdom the average life expectancy of women will be 91 years and men 88 years². Even though the ageing is a physiological process, the prevalence of diseases in group of elderly people is much greater than in general population. It has been shown that a 75 years old person statistically suffers from 3 or more diseases³. Interestingly, only 5% of people over the age of 75 in the United States in 2005 had no health visits⁴. Chronic kidney disease (CKD) is one of the diseases, which is characterized by increasing incidence with ageing. It has been shown that in the United States the prevalence of CKD is from 11% in general population and up to 30% among elderly persons⁵. The occurrence of CKD significantly increases the risk of death in elderly patient with diabetes, hypertension, heart disease or

stroke. CKD also reduces life quality⁶ by increasing risk of occurrence depression⁷ functional losses⁸, frailty⁹, falls and fall-related injuries^{10 11}, hospitalization and loss of independence¹² and cognitive decline¹³. Chronic kidney disease-generates also a significant costs to the health care system. It has been estimated that if dialysis is necessary, the average annual cost of treatment is from 70 thousand USA dollars in the patients aged 60-64 years to over 86 thousand USA dollars in patients over 85 years of age¹⁴. Taking into account the above-mentioned aspects it is important to pay special attention to this problem, because early diagnosis and treatment can improve survival, quality of life and reduce total cost of treatment¹⁵.

PATHOMECHANISM OF CHRONIC KIDNEY DISEASE IN ELDERLY

Changes that occur in the kidney during ageing can be divided on two parts namely: structural and functional. Structural changes include: decreased kidney weight

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and volume; glomerulosclerosis; cortical atrophy and loss of renal parenchyma; capillary tuft collapse; increased glomerular basement membrane (GBM); deposition of hyaline in GBM; change in GBM composition; interstitial fibrosis; tubular atrophy; intrarenal arteriosclerosis; thickened intima and obliteration of afferent and efferent arterioles^{16,17}. An autopsy study has shown that the number of glomeruli per kidney ranges from 250,000 to 1.5 million at birth and after the age of 18 the reduction of that number takes place with is about 6,752 glomeruli per year¹⁸. Other studies have shown a reduction in the weight of kidneys during the process of ageing from over 400g in 3rd and 4th decade to less than 300g in the 9th decade¹⁹. Denic et al. have analyzed 1638 living kidney donors. It has been shown that donors aged 18-29 years had a mean 990,661 non-sclerotic glomeruli per kidney in comparison with 520,410 non-sclerotic glomeruli in donors aged 70-75 years²⁰. It also has been shown that the number of completely sclerotic glomeruli in the group of elderly donors was more than 8 times higher. Other analysis of 1046 biopsy samples from donors has shown an increase in the percentage of sclerotic glomeruli with age²¹. The above mentioned changes lead to the loss of functional glomeruli and progression of CKD.

The functional changes in the kidney resulting from ageing include: decreased glomerular filtration rate (GFR); decreased effective renal plasma flow (ERPF); increased filtration fraction (FF); increased reno-vascular resistance (RVR); impaired water, electrolyte, and glucose handling; decreased diluting and concentrating capacity; renal vasoconstriction; decreased plasma renin activity and aldosterone; increased tissue angiotensin II and endothelin and decreased vasodilator activity of prostacyclin¹⁶. It is estimated that the average physiological reduction in eGFR per year is about 0.68 mL/min/1.73m² in men and 0.68 mL/min/1.73m² in women²². In individuals older than 40 years of age, eGFR decreases by about 1 mL/min/1.73m² per year. Decline in ERPF after that age is about 8 mL/min/1.73m²²³. Another study has shown decline in eGFR about 1.05 mL/min/1.73m² in individuals aged 70-110 years²⁴. The proposed mechanisms for ageing-associated renal disease are: oxidative stress; telomere shortening and loss off mitochondria; intrarenal activation of the renin angiotensin system; endothelial dysfunction; renal ischemia; increased renal TGF- β expression; accumulation of advanced glycation end products (AGEs) and chronic effects of uric acid.

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE IN THE ELDERLY

Chronic kidney disease is a major and growing health burden in Europe. One in 3 Europeans is at an increased risk of developing CKD. A striking 1 in 10 already has impaired kidney function severe enough to affect their health status. The current rise in diabetes, obesity and ageing will further worsen this situation unless there is greater focus and concerted action by European health policy-makers. Large population studies in different countries have shown that the prevalence of CKD range from 7% to more than 18%²⁵. It has been estimated that the average prevalence of CKD in the world increases with age and reaches almost 30% of individuals over 70 years of age²⁶. Impaired renal function (eGFR less than 60 mL/min/1.73m²) in group of individuals aged over 80 years occurs from 18,6% to over 50%²⁷. The Polish population study PolNef involving almost 2,500 participants has shown that the frequency of CKD is 18.6%. Almost 12% of studied population have albuminuria. Interestingly, it has been shown that nearly 70% of patients with CKD have also hypertension²⁸⁻³⁰. The first polish multi-disciplinary study of the elderly population PolSenior, which involve 5695 participants has shown that the prevalence of CKD in this group is nearly 30%. In group of individuals aged over 90 years CKD occurs in over 60%³¹. Interestingly, only 3% of subjects with CKD were aware of the presence of kidney disease. The study has shown the coexistence of CKD with diabetes, hypertension, prostatic hyperplasia, heart failure, coronary artery disease, the occurrence of myocardial infarction and stroke. Socioeconomic aspect also affects the incidence of CKD. It has been shown slightly higher incidence of CKD in the rural population, among people non-smoking and non-consuming alcohol. Crews et al. in observational study has shown a significantly higher prevalence of CKD among African Americans with lower socioeconomic status³². Such a correlation was not found in caucasians. Also, other studies have shown the negative impact of socioeconomic status on risk for CKD³³. In the REGARDS Study it has been shown that lower income is an independent risk factor for mortality in patients with CKD³⁴. Factors that combine low socioeconomic status with chronic kidney disease is certainly health-related behaviors like intensive alcohol intake, cigarette smoking, diet, physical activity, sedentary time; co-morbid conditions and access to healthcare³⁵.

RENAL REPLACEMENT THERAPY IN ELDERLY PATIENTS

The most common method of treatment of end-stage renal disease is renal-replacement therapy (RRT). It is known that starting hemodialysis treatment in elderly patients with CKD does not always bring measurable benefits. It has been shown that in elderly CKD patients without ischemic heart disease and extensive comorbidities RRT extends the lives³⁶⁻³⁸. Unfortunately mentioned above advantage is often associated with the deterioration of the quality of life, due to, among others, large number of hospitalizations³. Furthermore, it has been shown that initiation of hemodialysis therapy in the oldest group of patients (aged over 80 years) is associated with more than 50% mortality during the first year of treatment⁶. As it was mentioned above, the cost of renal replacement therapy in older patients reach over 86 thousand USA dollars per year¹⁴. The age of patients treated with RRT is steadily increasing. Incidence of dialysis therapy during last 10 years is decreasing but that of pre-emptive transplantations is clearly on the rise (more than doubled over last 10 years)³⁹. It is important because the life expectancy of dialysis patients is reduced by two thirds compared with the general population and that of transplant recipients by 25-30%⁴⁰.

CONCLUSIONS

Comorbidities and lifestyle often exacerbate the physiological ageing process of kidney. CKD occurs frequent in elderly population and its prevalence range from 30 to 40% of individuals. Considering the ageing of the population and the increasing prevalence of diabetes, hypertension and obesity it seems that the incidence of CKD will be increasing in coming years. The prophylaxis and treatment of CKD should take into account potentially modifiable factors like health-related behaviors, comorbid conditions, and health-care access. It should be noted that lower socioeconomic status might lead to poorer self-management and thus greater complications from systemic disorders like diabetes or arterial hypertension. Socioeconomic factors seem to be a suitable target for interventions at the national and supranational level aimed at reducing disparities in CKD. The age of patients treated with renal replacement therapy is steadily increasing. It should be remembered, however, limited benefits of renal replacement therapy in the group of oldest CKD patients.

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REVIEW

The centenarians surgery

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Background. The increase in life expectancy makes surgery for old people a routine. In addition, a quest to develop technology and guidelines for centenarians is now emerging.

Ethical issues. Surgery cannot be refused neither because of chronological age of the patients nor on economic grounds.

Consensus. Surgeons are requested to make the right choice in the right way by pondering on health related quality of life, by obtaining the help of other professionals, and after having ascertained the integrity of the neurological conditions. Family opinions not legally relevant.

Key words: Surgery, Old age, Centenarians, Health related quality of life, Chronological age, Valid informed consent

INTRODUCTION

“Senectus ipsa morbus / Old age is a disease”
Terence

“Senectus quamvis non sit gravis, tamen aufert viriditatem/ For even though old age may not be a burden, it yet impairs the strength”
Cicero

“The mortality of life is 100 per cent”
Rhoads

“How much a doctor should do for aged patients?”
This question briefly summarize today’s medicine main problem and it is a topic full of contradictions regarding legal, scientific, ethical and economic issues.

This work wants to offer some handy to use contents in the current debate and “to mend” professional relationships between experts with a different proficiency.

Performing surgery on centenarians could seem risky,

almost irrational. Nevertheless, our considerations will show how this choice could be a result of precise clinical and ethic evaluations.

CLINICAL CONSIDERATIONS

A fundamental question is: how can we define a patient as “aged”? Everyone agrees that biological age is more important than chronological age^{1,2}, but for a statistical purpose it is better to define a cut-off point considering the life condition of our society. Even if a worker could be defined as “old” at age of 65/67 (the usual retirement age) a more reliable cut off should be 70 years old.

The increase of life expectancy brings a greater rate of pathologies in aged patients, especially oncological ones^{3,4}. Almost 60% of new cases of cancer are found in people over 65 years old and about 40% is found in people over 70 years old. If we consider rectum cancer, the mean age of the diagnosis is 68,4 years while for colon cancer it is 70,5 years with a progressive increment until the eight decade. In other words, almost

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50% of deaths for colorectal cancer are found in people over 75 years old.

Generally, the evaluation process that brings a patient to surgery is not different between an 80-year-old patient and a 50-year-old patient. Indications to surgery should follow these parameters ⁵:

- clinical conditions of patients (biological/chronological age, PS, ASA score...);
- chance of successful surgery;
- health related quality life before and after surgery;
- elective surgery/emergency surgery;
- chance to express a valid informed consent.

However, many factors should be considered in the surgical decisional process on aged patients. Obviously, there is not much to talk if we have a conscious patient in good health with rectus cancer or lower limbs gangrene ⁶; but if we have an aged patients with several comorbidities and different problems related to the social context, the decision making process should take account of ethical and moral aspects too ⁷.

It is important to consider life quality related to health status of patients: the “health related quality of life” (HRQOL). In fact, the aim of surgery for aged people should be quality of life as well as survival. All risks of surgery and peri/post-operative complications should be evaluated (e.g. ictus, loss of consciousness) because they could have a catastrophic impact on QOL, with loss of autonomy and further need of assistance after hospital discharge.

Somebody believe that below certain values of quality of life ⁸, life is not worth to be lived. So, if there is no chance to get back a good value of HRQOL, surgery should not be proposed. However, as Rhoads said “*Life has 100% mortality, death is inevitable*”. Today’s medicine should be focused more on QOL instead of death prevention ⁹, which had been her main objective for centuries. There is no real virtue in living forever! Anyway, even the HRQOL needs to be evaluated with cautions: surely, if the surgeon believes that there is a high chance of success, he will promote the surgery, especially in emergency situations; on the contrary, if there are low chances of success and the surgeon wants to abstain from surgery, he must discuss his choice with the patient accurately ¹⁰.

The decision should be made each time in order to look for best benefit for the patient, and we are sure that even in the most complex cases, the experienced surgeon is the most qualified person to make this decision, more than patient family or judges.

In more complex cases, we find useful to stick to these 3 rules:

- perform an evaluation of functional and neurological state of the patient before the acute event;
- use a multidisciplinary approach, sharing

responsibility with other professionals such as geriatrist, psychiatrist, gastroenterologist, physiatrist;

- remember that family attitude, even if not legally binding, it is fundamental for the therapeutic approach for patients who cannot express a valid and informed consent ⁷.

We know that family opinions are not legally relevant and cannot stand for patient will, despite it seems correct for us to acknowledge family will.

ETHIC ASPECTS

Could surgeons refuse to perform surgery on a patient in good health (considering old age) just because life expectation cannot be extended further ^{11 12}?

This question has two different answers. The first answer is that they do not; in fact, this choice would imply the violation of responsibility parameters of medical profession. Moreover, we should consider that a doctor does not have rights to exclude the use of surgery – if it is technically possible and can reasonably bring to a success ^{13 14} – just because probably the patient will not live any longer, since his old age. If we start from such assumptions, we could deny the chance of survival of a large number of patients.

Anyone who follows the ethic debate about caring in the old age has surely noticed that patient’s “age” is considered a “therapeutic indicator”, like a discriminating parameter to decide if we should assist or not the aged patient using expensive procedures or surgery ¹⁵. If age could be a useful parameter to evaluate the outcome of a therapy, it could not be the only parameter to define a risk-benefit calculation. This kind of evaluation would translate into an interest to perform procedures only in patients who, once recovered, would be useful and productive for the society.

The appearance of this “ethical utilitarianism” in the health-care environment suggests as primary standard the calculation of results such as capability and productivity in a lifetime, a reductive and anti-personalist vision of the quality of life concept. So, whoever needs more help because of age or disability, such as elderly people, is penalized instead of being supported.

The personalist principle instead considers the single person more important than science and community interests, and this should be considered the main reference when taking care of patients. In this context, human life is considered as an inviolable value itself; old people are no more reputed as parasites for our society, but as a value, so that they are not excluded. Conversely, the community should improve social, cultural and creative involvement of elderly people. Adopting this principle assumes to evaluate social consequences of

this clinical decision, in order to share advantage and disadvantages equally.

Because health value is necessary, it is also indispensable for every single person to be co-responsible. Well-being is a necessity as such as should be managed, adopting well balanced life styles, not abusing of drugs and not undergoing useless procedures and treatments that pinch resources to whom really needs them.

Guided by these principles, we retain that the health service, considered as organization and use of available resources, should look at the criteria of sociality and subsidiarity, according to which elderly people must be treated on the basis of their necessities, without discounts. Physicians behaviour towards elderly, fragile and sick patient should be levelled out to the same criteria used for every medical practice^{16 17}: choosing the most appropriate therapies (evaluating the risk-benefit correlation) and proportioned to the clinical case; requesting the informed consent; humanizing treatments. But this is not taken for granted. Talking about health service means discussing about limited resources, and their use is influenced by social culture, that considers elderly people in a negative way. In the international environment it has been discussed about the risk of distinguish treatments along with the chronological age. The supporters of reduced quality treatments for elderly people assert:

- elderly people should quit sanitary assistance in order to support youth people assistance;
- society should use less resources for elderly people, in order to use more for youth people;
- if medical treatments must be rationed, it is more fair to ration them concerning the chronological age.

Opposing to these thesis, another group of people asserts:

- chronological age is an arbitrary and unsuitable parameter; elderly people are a heterogeneous group and many of them could live longer life when treated in a right way;
- needing is the best parameter for health service distribution: elderly people need more treatments as they have higher risk of inability or getting sick;
- decisions concerning therapies should be adopted exclusively basing on physician's evaluation, together with the patient and his family.

Chronological age parameters, as well as a determining index to establish how to use resources for health service, has been debated for a long time^{1 5 10 17 18}. Although it has not been officially adopted in any country, it has effectively been applied as a reference point, unofficially. For example, many medical centers practicing heart transplants in US do not accept patients over 50-55 years old. The same parameter is applied

for dialysis treatment and kidney transplants in those countries where resources are limited. Particularly, since many years, in UK patients are excluded basing on the age: patients older than 55 years old are reasonably excluded from therapies.

Also for micro-allocative selections at patient's bedside, chronological age finds many agreements: for example, in intensive care units, when it is time to decide to whom to assign the only seat available, it is usually given to the younger patient.

This does not mean that chronological age should never be considered as a selective parameter: instead, it should not be considered as the only one, but as a susceptible parameter to invalidate, totally or partially, medical benefit connected to the treatment. In other words, chronological age constitutes a useful factor to establish proportionality judgment so that, when it is inevitable the comparison between different patients due to shortage of resources, to establish a major or minor "benefit probability" connected to the treatment. Therefore, if the evaluation of therapeutic proportionality will lead to select and treat the younger patient, disadvantaging the older, this choice will not be the result of a preliminary criterion, but it will be based on different therapeutic chances connected to specific clinical situations of the two patients.

FINAL CONSIDERATIONS

In the era of knowledge and benefits due to progression, paradoxes and contradictions of medicine are underlined, forced by economical restrictions preventing the usage of technological and innovative treatments: so, which are the parameters that physicians should keep in consideration? If in the past, in fact, medical treatment was only guided by the patient benefit, or rather by the clinical interest (paternalistic model), nowadays in the actual ethical context the physician must "make the right choice", "in the right way", according to science, according to patient, and also, according to collective parameters. Guidelines, always more often invoked, can provide a useful reference point to better act respecting economical parameters, but remembering that health care service cannot be administered exclusively based on financial and administrative logics, but it should be based on patient's centrality and humanization of treatments.

It is therefore indispensable to reaffirm the authentic meaning of medicine, meant not as the mere restoration of human body, but as the whole safeguard of human health. Therefore, we retain that the physician cannot and should never be a passive executor, but also he should not be left alone when leading with high complexity situations.

Different elements making every choice difficult, and not without enormous risks loom over physicians, regarding if and how to act, and particularly over surgeons. Very often they find themselves in a real grip: on one side, patients' inclination to criminalize any clinical choice which can lead to unsatisfactory outcome; on the other side, the fear of legal issues (malpractice); in the end, hospital management pressure to reduce costs against the clinical needs and the safeguard of patients' health. Physicians are increasingly left alone.

We need to create conditions for a "great pact" of collaboration between physicians, citizens, administrators and politicians, to give an answer to the new and increasing healthcare needs in a redefined ethical and normative contest.

We conclude remembering the teachings of Immanuel Kant (1724-1804). In *Grounding for the Metaphysics of morals* (he wrote "Act in such a way that you treat humanity, whether in your own person or in the person of any other, never merely as a means to an end, but always at the same time as an end"). Translated by Ellington, James W. (3rd ed.). Hackett. 1993, p. 36. 4: 429 ISBN 0-87220-166-X).

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REVIEW

An aquatic organism as time machine: *Nothobranchius furzeri*

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Background. There is need for animal models to study ageing. Worms, flies and mice have been extensively explored with outstanding results.

Aims. Many studies have used *Nothobranchius furzeri* - the African turquoise killfish with a lifespan less than 1 year.

Results. Studies have shown that the ageing process of *N. furzeri* and humans share many features.

Discussion. Despite its relatively short lifespan for a vertebrate, *N. furzeri* shows many molecular, cellular and physiological ageing phenotypes, shared with many other organisms, including humans. We have shown a significant impairment of learning performance with age, when tested using an active avoidance task.

Conclusion. *N. furzeri* is an ideal model to explore – in short time – molecular mechanisms that control ageing in vertebrates, including humans.

Key words: Animal models for ageing, *Nothobranchius furzeri*, African turquoise kill fish, life span, Eastern Africa

INTRODUCTION

The usefulness of biological models in improving the understanding of disease mechanisms, diagnostics and treatment is undisputable. According to the definition of Wessler, an animal model is “a living organism in which normative biology or behavior can be studied, or in which a spontaneous or induced pathological process can be investigated, and in which the phenomenon in one or more respects resembles the same phenomenon in humans or other species of animal”¹. The three traditional multicellular model species for aging research (worms, flies, and mice) have been thoroughly studied. Breakdown in the maintenance of genomic stability, stochastic damage to DNA, and inadequate repair processes, as well as oxidative damage and impaired protein processing and folding have been widely implicated in their aging. Dietary restriction (DR) appears to prolong life span in all classical models. Similarly, single-gene mutations that alter life span have been identified in yeasts, worms, flies, and mice. Furthermore, a similar

genetic mechanism and a concomitant biochemical pathway have been found across the phyla. However, there is an animal model, *Nothobranchius furzeri*, which is known as the vertebrate with the shortest lifespan ever described in captivity, representing a powerful and useful animal model to address key question on how organisms age and which are the mechanisms underlying the age-related diseases.

In the present manuscript, I intend to recapitulate all the main relevant biological characteristics which make the annual teleost fish *Nothobranchius furzeri* an excellent model for ageing studies in biomedicine. Research into ageing in vertebrates is hampered by the lifespan of available model systems and tractable laboratory species with a lifespan of less than 1 year are highly desirable. This fish has a naturally compressed life span and short generation time, and shows typical signs of ageing according to the worldwide accepted definition. Ageing is indeed described as ‘a progressive, generalized impairment of function that results in a loss of adaptive response to stress and an increasing

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*probability of death*². In the natural world, ageing is characterized by an increase in mortality and decrease in fertility. Ageing is a consequence of damage, through the gradual accumulation of faults in molecules, cells and organs, leading to loss of physical, cognitive and immune function, and increased frailty and vulnerability to age-related diseases.

LIFE CYCLE OF *N. FURZERI*

Nothobranchius furzeri, also known as African turquoise killifish, inhabits seasonal pools which are formed during the monsoon season in the Eastern Africa. Currently, two strains are available in laboratory conditions: GRZ and MZM. The GRZ strain has the shortest recorded lifespan with a median lifespan ranging from 9 to 16 weeks³ depending on the culture conditions, whereas MZM are considered as longer-lived strains, with median lifespans ranging from 23 to 28 weeks⁴.

The short life cycle is due to the adaptation to the ephemeral and unpredictable conditions of the natural habitat, characterized by the alternance of dry and wet season. It has adapted to the routine drying of their environment by evolving desiccation resistant eggs that can remain dormant in the mud for one and maybe more years as embryos encased in the dry mud⁵. This delay in development is accomplished by the eggs entering into diapause where oxygen consumption is depressed. When it rains, the embryos hatch and reproduce in the few weeks before their habitat disappears. Therefore, fish rapidly hatch, grow rapidly and become sexually mature within three weeks, and reproduce before the dry season. This fish maintains its compressed life span and short generation time in the laboratory, when water is in constant supply. Accelerated maturation is observed in captivity as well; growth and maturation are accelerated even when compared with other, longer-living, species of the genus which originate from more humid climates with longer rain seasons.

Despite its relatively short lifespan for a vertebrate, *N. furzeri* shows many molecular, cellular and physiological ageing phenotypes, shared with many other organisms, including humans.

AGEING PHENOTYPES

Similarly to ageing mammals, who progressively lose hair and skin pigment with age, male *N. furzeri*, which are more colorful than females, progressively lose body and tail colour. Old age in this short-lived vertebrate is also associated with emaciation, abnormal spine curvature, defective vision, fin structure deterioration. At

a behavioral level, there is a generalized reduction in spontaneous locomotor activity, with older *N. furzeri* individuals spending less time exploring compared to young ones; a significant impairment of learning performance with age, when tested using an active avoidance task⁶.

AGE-RELATED MARKERS IDENTIFIED IN *N. FURZERI*

Several ageing biomarkers have been identified to characterize the physiological age of this teleost fish. Lipofuscin, a yellow-brown autofluorescent pigment whose concentration increases with age in several species, including humans, accumulates in the brain and liver of old *N. furzeri*. Senescence-associated β -galactosidase (SA- β -gal) staining, a marker for cellular senescence and stress response in human cells, significantly increases in the skin of aged fish. Neurodegeneration – measured by Fluoro-Jade B, which stains cell bodies, dendrites and axons of degenerating neurons – increases in fish brains from as early as 2 months of age, strongly suggesting a spontaneous age-dependent increase in neurodegeneration. Spontaneous neoplastic lesions have been observed and measured in *N. furzeri* strains using several tumor-associated proteins, including Bcl-2, cytokeratin-8, carcinoembryonic antigen and mutated p53.

Histopathological examinations have revealed the nature of age-related organic decay: kidneys undergo tubule dilatation and crystal deposition; cardiac lesions ascribable to hypertrophy of the cardiomyocytes; age-dependent liver lipid accumulation.

At the molecular levels, the major changes described are: age-dependent telomere attrition; reduced mitochondrial numbers (as assessed by mtDNA copy numbers) and function, especially in liver, muscle and brain. Age-related capacity to regenerate the caudal fin after amputation in the long-lived MZM - 0703 strain has been documented⁵.

EXPERIMENTAL MODULATION OF LIFESPAN

N. furzeri lifespan and ageing have been experimentally modulated through external intervention such as diet, temperature and chemicals supports, indicating that this organism can be used as an experimental platform for large-scale screens of age-modulating genes and chemicals.

The effect of dietary restriction (DR) has been tested in both strains of *N. furzeri*, which were fed every other day instead of daily. The results were strain-dependent: DR resulted in prolonged lifespan in the short-lived GRZ

strain but not in a wild-derived, long-lived MZM-0410 strain. Under the DR regimen, the short-lived strain showed reduced neurodegeneration, slower accumulation of lipofuscin, improved learning performance and decreased occurrence of tumours ⁷.

Lower water temperature extends both the median (1 week) and maximum (1.5 weeks) lifespan of *N. furzeri*. Furthermore, it leads to a 40% decrease in adult size compared to control animals grown under regular culturing temperature, suggesting a dramatic influence of temperature on metabolism. Several age-associated phenotypes, such as lipofuscin accumulation, spontaneous locomotor activity and learning performance, are also significantly improved in fish cultured at a lower temperature ⁸.

The supplementation of the natural polyphenol resveratrol, known to increase lifespan and delay ageing in several invertebrate and vertebrate organisms, can increase median and maximum lifespan in a dose-dependent manner in both male and female *N. furzeri*. In addition, compared to control-fed fish, resveratrol-fed fish are physically active for a longer time, and display late onset of typical ageing phenotypes ⁹.

GENOMIC AND TRANSCRIPTOMIC RESOURCES

The sequencing of the genome and a large number of transcriptome data (i.e. which genes are switched on or off during the process of aging) are now publicly available to the research community. By comparing the ageing process at different tissue levels (i.e. brain, liver and skin), it has been found out that genes responsible for ageing in *N. furzeri* are not spread randomly, but rather, are concentrated into specific small regions of the genome ¹⁰. The discovery of these ageing hot spots in the genome let assume that the genes within these regions are somehow coordinated in their activation or de-activation. In addition, knowing how ageing-relevant genes are organized and how they can be (in)activated can help to identify key mechanisms regulating human aging as well.

Analysis of whole transcriptomes of the two strains, GRZ and MZM-0403, supported the difference in ageing pace between these strains. When comparing time-normalized fold changes of identified differentially expressed genes, age-related transcript level changes are stronger in GRZ than in MZM-0403, confirming previous findings, based on the analysis of age-related biomarkers, showing that ageing is accelerated in the short-lived strain GRZ compared to the longer-lived strain MZM-0403 ¹¹.

GENETIC MANIPULATIONS

Efficient and reliable ways to generate precise changes to the genome of model organisms have been a long-standing goal of discovery-based and translational research. Protocols providing powerful genetic tools for studying vertebrate ageing and aging-related diseases in *N. furzeri* are available. By taking advantage of the clustered regularly interspaced short palindromic repeats/CRISPR-associated protein-9 nuclease (CRISPR/Cas9) system and the *N. furzeri* genome, it is possible to enable the generation of knockout alleles via non-homologous end joining (NHEJ) and knock-in alleles via homology-directed repair (HDR) ¹². There are also available strategies for Tol2-based transgenesis, to generate transgenic *N. furzeri* that express green fluorescent protein with germline transmission of the integrated transgene ¹³.

Both these methods are rapid and highly efficient, permitting generation of stable transgenic lines more rapidly than in any other available vertebrate model.

CONCLUSIONS

In conclusion, the ageing process of *N. furzeri* and humans share many common features, both being vertebrates. More importantly, for those researchers who use *N. furzeri* as a model system, the sequencing of its genome and a large number of transcriptome data (i.e. which genes are switched on or off during the process of aging) are now publicly available to the research community. Several studies over the last decade have shown that, in many aspects, ageing in *N. furzeri* resembles mammalian ageing. In addition, the existence of several natural strains with different lifespans and the possibility of engineering the genome as well as the recent availability of its genome sequence have helped *N. furzeri* become an accepted model for ageing research. It is indeed an ideal model to explore – in short time – molecular mechanisms that control ageing in vertebrates, including humans.

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REVIEW

The Human Capital of Age

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Aims. To study the contribution of old scientists and artists to the Human Capital of Age.

Methods. We have studied the Human Capital of Age in university professors, scientists and artists. We have analyzed the answers to questionnaires of 99 professors in 99 universities of 20 countries with diverse gross domestic product (GDP), and the 10 most important discoveries in medicine in the years 1453- 1953 all made by young scientists.

Discussion. The best teams are made by old and young scientists, supervised by a young coordinator.

Conclusion. The best solution to the problem of ageing scientists is that practiced in USA where tenures are for life and merit is the first goal of the scientific enterprise.

Key words: Creativity, Emeriti, Retired professors

THE CREATIVITY OF EMERITI AND RETIRED PROFESSORS

Recent data have shown that emeriti or retired clinical professors of 99 universities in 20 countries of high, low and intermediate GDP continue to be very productive and their creativity is marked by a constant scientific output¹⁻³. It was shown that more than 40% of them continue to publish a relevant paper or book per year after retirement. The authors of those studies also noticed that many emeriti or retired professor produced up to 7-11 papers per year. Because of their role, in many universities, they were granted benefits in terms of genuine office, phone, fax, parking, access to libraries and labs, participation to the assembly of the department and of the University, representativeness of the dean and the president. Teaching was allowed in all forms: normal courses, seminars, tutorial courses as well as courses for master and Ph. D.

In USA, Canada and Australia *emeritus (a)* professors continue to work in the departments where they have worked lifelong, they can apply for private and public

grants and act as principal investigators⁴. In the United Kingdom the age for retirement is fixed at 65, but a 3 year prolongation is now the rule, and probably 3 additional years will be soon allowed. We do know that in UK, people would like to retire by mid-seventies⁵.

In USA chronological age is not a factor to withdraw from a job⁴ and the value and the role of older investigators for the scientific enterprise of the Country is fully understood and appreciated. University tenures are not age limited, although there is evidence that old scientists prevailed over young scientists in obtaining grants from the National Institutes of Health in the years 1980-2010. This is certainly a case for concern. But as expected from a country where merit has a priority all efforts are made in order to allocate correctly the applications for public grants. A change toward forbidding applications of older scientist as principal investigators is not into discussion. Possible incentives however are being scrutinized and discussed in order to force old scientists to help younger fellows in their grant applications, probably by reducing the burden of other duties which are currently imposed on the older scientists like

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teaching and administration. This tutorial work is seen as indisputable in order to preserve the rank of USA in science. A rank which has been achieved and maintained through tax payers.

At the Carnegie Mellon University - 19 Nobel Laureates, mainly in economics, physics, chemistry, highly ranked in computer science (1st in 2010) *emeritus(a)* professors:

1. continue to be a member of the university and of their academic departments, participate in the department/faculty meetings as before retirement but without vote;
2. are assured reasonable office space (a genuine office) when needing it;
3. serve as primary/principal investigator on grants, supervise doctoral students and have full access to email, libraries, and interlibrary loan privileges and to benefit from grants programs.

At Cornell University, Ranking 19 - World University Ranking 2014, *emeritus(a)* professors:

1. have the right to a Cornell identification card stating their role;
2. have access to libraries and library resources, mail services, parking, the central computing system, to athletic facilities, and are listed in the university telephone directory;
3. can enrol and attend classes free of charge, subject to space availability, have legal defence and indemnification with respect to claims that arise from authorized duties, may act as principal investigator (conditional on the availability of department resources) and are voting members of the university faculty, being eligible to serve on elected or appointed university faculty committees.

At the University of Yale, ranking 10th - 11th in world rank the Henry Korner Center assists with the arrangement of teaching assignments for those interested in teaching, in continuation of research and scholarly writing and to promote small grants for these activities, as well as in receiving instructional assistance with computer problems.

At the University of Texas at Austin, holders of the *emeritus* title are accorded membership (without vote) in the general faculty and in the college and department faculties in which membership was held previously, to serve in graduate committees, to make use of the campus mailing service, to have a listing in the faculty directory, to have office space with the approval of department chair, dean and vice-president.

At the University of Virginia *Emeritus* professors may continue to be active members of the university community, depending on the needs of their schools and the individual faculty member's preference. They may be employed part-time or work as unpaid faculty. To foster this continued role, they:

1. continue to be members of their academic departments and will be listed as such in directories;
2. may attend and participate in university and faculty meetings without the right to vote;
3. they are retained in all mailing lists, have access to (a) electronic mail, (b) university libraries and (c) interlibrary loan services; they may request permission from their dean to serve as principal investigators on grants subject to the PI application process;
4. they request permission from their dean and department chair to continue to supervise doctoral students or teaching on a part-time basis;
5. they are entitled to have access to university grants to retired faculty members;
6. they may participate in the university ceremonies and march in a position of honour in academic procession.

At the University of Queensland in Australia (World Rank 47), the title is conferred for an unspecified period by recommendation of the head of schools and approval of the Vice Chancellor, on professional staff who have served the university in an outstanding manner. It is not a normal expectation of professors who leave or retire and can be withdrawn by the Vice Chancellor, without appeal, when it is no longer in the best interests of the university. *Emeritus(a)* professors can use university libraries, have an email address, use facilities and resources of the unit as appropriate, can be appointed to research, take on higher degree student supervisory or advisory roles, and have access to support for applications for grants and funding. They have access to internal research support, and it is expected that they will list the university in the by-lines of publications. They can be elected in committees (with exception of the academic board), and are covered by a personal accident insurance. They can supervise students, apply for research grants, and access university resources including parking. All activity is in a voluntary capacity, however compensation may be granted while acting on behalf of the university.

AGING ASSOCIATED WITH BETTER HEALTH

According to recent studies of the National Institutes of Mental Health and of the Sam and Rose Stein Institute for Mental Health at the University of California San Diego ¹¹, "*aging is associated with better mental health despite loss of physical and cognitive function*". The study analyzed happiness, satisfaction with life, depression, anxiety and wrong decisions. According to Dilip V. Jeste-senior author of the paper – which was based on a cross section study in 1546 persons aged 21-99 years – aging people without disease do well. When a disease is present, depression may affect older

persons, but it is treatable with success. In absence of disease the mild cognitive decline is not a case for concern. The study concludes that thinking that older people are affected by disability, loneliness, social isolation and cognitive decline is a misconception. Indeed the study disclosed the better capability of older persons to cope with adversities ¹².

ON RETIRING SCIENTISTS

In 1963 Derek J. de Solla Price in *Little Science Big Science* ⁸ wrote “we can say that 80 to 90% of all scientists that ever lived are alive now”. Alternatively, any retiring scientists looking back at the end of his career upon a normal life span will notice that 80 to 90% of the scientific work has taken place before his very eyes. He analyzed the doubling time of the number of the journals and calculated it in 15 years, whereas that of the number of papers was 10 years. Finally, the doubling time of the number of the scientists was in the range 10-15 years. It means that “every retired scientist is a walking, living, eye-witnessing historian of most of the science that has molded his or her discipline” ⁹. Science has an impact on economy. “Since science grows at twice the rate of economy, it is necessary to do 4 times as much science to get twice as rich”. Price – although considered a founder of scientometrics, bibliometrics and impact factor – denied any value to the measurement of research: “evaluating research is a nonsense”.

In addition, he analyzed the migration of scientists from poor to rich countries and was the first to speak of brain drain ⁹. He was also precise in identifying the invisible colleges “each consisting of a microdiscipline of few hundreds of researchers who understand the field and its, unpublished lore”.

RETIRE RETIREMENT

“Retire retirement” is the title of a commentary that Professor Peter A. Lawrence of the Department for Molecular Biology at the University of Cambridge in UK, wrote after interviewing many aging scientists ¹⁰. Lawrence put emphasis on the fact that in USA, Australia, Canada and partly and slowly in United Kingdom age does not discriminate those asking a work place. Abolishing discrimination for age as well as that more traditional for women “ensures dignity and justice within the enterprise of science... The effects of compulsory retirement are multiple and insidious. ... it turns able academics into lame ducks: they cannot take on commitments such as graduate students and they lose their negotiating power because they cannot seek new posts”.

He praises the achievements in USA where due to the pioneer bill of senator Claude ‘Red’ Pepper many discriminations were abolished including that of age.

“In the United States, older scientists make various contributions. Some are great role models and mentors, some augment the international reputation of their institutes, some teach or administrate, freeing younger scientists. More importantly they can provide a deeper perspective on scientific strategy”. He also asks to evaluate the contributions of people not just by counting the papers or by undergraduate ratings on teaching. In fact many scientist have lack enthusiasm even in their thirties, whereas many other are still enthusiastic in their seventies. Abolishing discrimination for age affirms “the right of every individual to be considered for work on merit and negotiate for remuneration”.

Megan Scandellari interviewed scientists about retirement from university positions, and on the handing their experience to the younger scientists, since in the years 1998-2014 the proportion of grants awarded to scientists older than 65 went up to 4.8% to 12%, thus it might be conducive to a limitation of availability of opportunities for young scientists. One solution might be the institution of an emeritus award to encourage the handing over of projects to junior faculty members ¹¹.

That is to say that if one has not found the phoenix in a career of 40 years one should not ask for prolonging it. It is the case to remember that the mythical phoenix (fire-bird) was able to rebirth from its ashes every 500 years.

Her answers cover a wide range of attitudes. The first is that of people who want to retire as early as they can. “Only do things I really feel passionate about. That’s the beautiful luxury of retirement”. “Stopping does not mean stopping, it means do what you have always wanted to do”. “The ideal would be that no one checks how old you are but just look at what you are doing and what you are able to do, but the idea hasn’t pervaded into the public routine”. For many scientists, “working after 65 is working because you want to, not because you have to”. “It is not understandable to force people to retire when they are still contributory” ¹¹.

Furthermore, just there is no or not enough evidence that early retirement can reduce unemployment, particularly youth unemployment since some studies show the opposite. Paying senior people to retire may indeed increase unemployment. In fact, there are no fixed jobs in economy. Indeed when women entered finally the market of jobs in the last century the newly emerged two-earners family lead to an increase in the number of jobs ¹¹.

THE PATRIARCHES BEFORE THE FLOOD

The Genesis reports the roll of Adam’s descendant ¹². “When Adam was a hundred and thirty years old he

fathered a son... and he called him Seth. Adam lived for eight hundred years after the birth of Seth and he fathered sons and daughters. In all, Adam lived for nine hundred and thirty years, then he died".

"When Seth was hundred and five years old he fathered Henosch. After the birth of Henosch Seth lived for eight hundred and seven years, and he fathered sons and daughters. In all Seth lived for nine hundred and twelve years, then he died".

We omit the complete list and go directly to Noah who was born from Lamech at the age of hundred and eighty-two years. *"After the birth of Noah Lamech lived five hundred and ninety-five years and fathered sons and daughters. Noah in turn when was five hundred years old fathered Shem, Ham and Japhet".*

From this concise description we learn that patriarches were long-lived and fertile nearly to the end of their life and *"fathered sons and daughters"*.

GULLIVER IN THE COUNTRY OF IMMORTALS

In his travels ¹³ Gulliver reached the Kingdom of Lugnagg, a country where immortals (*struldruggs*) live. Every child has the chance (the risk) to be immortal. The immortals are easily identified by a red round spot on the forehead, over the left eyebrow. A sign indicating that the person will not die but not indicating eternal youth. Their total number exceeded thousands and because of the risk that they might waste the economy of the country at the age of 80, they are deprived of all their properties which are handed to their heirs, and are granted a modest pension scarcely covering their needs. Thus, they are pushed into poverty. At 90 years of age they lose their hairs and their teeth, have difficulty in understanding the changes of the language. Furthermore, their mental capability collapses, their memory vanishes. They do not even remember the beginning of a phrase when during a reading they reach its end. With advancing age, they become horrific. And women were more horrific than men. According to Gulliver, their simple presence removed the fear for death.

AGING IN OUR GLOBAL WORLD

According to a census, in the present time live some 451,000 centenarians. Only 96,000 belong to the male gender. In Italy live 3 people aged more than 110 years. We do also know that children born after the years 2000 have the possibility to live 105 years. It is foreseen that half of them will reach the 100th birthday ¹⁴.

Artists usually anticipate events which will become of age at a later time. This fits very well with a book

(*Modern death*) authored in 1976 by the Swedish writer Carl-Henning Wijkmark ¹⁵. The novel reports on a congress organized by the Swedish Ministry of Health with the goal to reduce the access of old people to health services. This is badly needed in a period of crisis, prolonged lifespan, and early retirement. *"The problem is that one of four Swedish people is pensioned because of age, and one out eight productive persons is allowed to retire in advance. Thus 75% of health expenditure is utilized for chronic disease and patients without hope"*. The debate was dramatic and driven by politicians, theologians, economists and physicians. There was agreement that, in order to save the welfare of the country, old people should accept to anticipate their death and let their bodies to be used as spare parts for organ transplantation and as fertilizing compounds. The families are requested to not oppose to the decision which foresees a 100% use of the bodies by the chemical industry. *"Aging persons are classified according to their productivity and social value. Of course a Nobel Laureate is in the highest rank"*.

Wijkmark surely had not read *Cato Major de senectute* of Marcus Tullius Cicero (Arpino, 106 a.C. - Formia, 43 a.C.) who was please to underline *"that there is also the tranquil and serene old age of a life spent quietly, amid pure and refining pursuits, such an old age, for example, as we are told was that of Plato, who died, pen in hand, in his eighty-first year; such as that of Isocrates at the age of ninety-four authored Panatenaicus and that his mentor Gorgia of Leontini completed 107 years and did not discontinue his studies and his work"* ¹⁶. He was of the idea that old age does not impede or maintain our own duties, as in the youth and one does it with more success.

"Those, therefore, who allege that old age is devoid of useful activity adduce nothing to the purpose, he may not be doing what younger members of the crew are doing, but what he does is better and much more important. It is not by muscle, speed, or physical dexterity that great things are achieved, but by reflection, force of character, and judgement; in these qualities old age is usually not only not poorer, but is even richer".

"Old age withdraws us from active pursuits." From what pursuits? Is it not from those which are followed because of youth and vigour? Are there, then, no intellectual employments in which aged men may engage, even though their bodies are infirm"?

"And, indeed, when I reflect on this subject I find four reasons why old age appears to be unhappy: first, that it withdraws us from active pursuits; second, that it makes the body weaker; third, that it deprives us of almost all physical pleasures; and, fourth, that it is not far removed from death. Let us, if you please, examine each of these reasons separately and see how much truth they contain".

RICH PEOPLE ARE HEALTHIER AND LIVE LONGER

Rich people are healthier and live longer. In United Kingdom the specialists by reading the postal code may identify the persons who will live 11 years below the nation's average. In Turin those who live in the mythical hill, where also the Agnelli family lives, lifespan is 4 and half year longer than for those living in the suburbs of the city.

In Washington, following the path of the metro-line departing from the quarters settled in the South-East – where poor families live – and moving to the rich County of Montgomery where rich people have their houses, for every mile the lifespan of the inhabitants increases by 18 months, for a total between the two ends of nearly twenty years. In other words according to the quarters one lives the 53-58 years or 73 or more ¹⁷.

INNOVATION AND EPOCHAL IDEAS: ARE OLD SCIENTISTS DETRIMENTAL TO THE PROGRESS OF SCIENCE?

If one analyzes the 10 greatest discoveries in the years 1453-1953 departing from Vesal (*De humani corporis fabrica*) to Maurice Wilkins (the double helix), if we include William Harvey, Antony Leeuwenhoeck, Edward Jenner, Crawford Long, Wilhelm Roentgen, Ross Harrison, Nikolai Anichkov, Alexander Fleming, it becomes evident that their mean age at the time of discoveries was 32.4 years, however Vesal, Long and Anichkov were just twenty years old, whereas Maurice Wilkins *floruit* at 38 years of age ¹⁸. That is to affirm that young people bring the innovation in the scientific enterprise, however a team made just of young people lacks diversity which is indispensable to stimulate creativity. In a team, the lack of diversity (only young scientists or only old scientist does not make a difference) reduces the quality and the quantity of the output. The best results are obtained when young people work together with old people who bring the experience ¹⁹, this renders possible to birth of epochal ideas when the coordination of the team is made by a young scientist. When the coordination is in the hands of old scientist this outcome is not granted since old scientists tend to enroll old scientists ¹⁹.

The Nobel laureate Rita Levi Montalcini ²⁰ did not agree with Simone de Beauvoir and Norberto Bobbio who looked at ageing people with repugnance. In fact “*human brain is provided with a great potential even in old-old people which is greater than those usually acknowledged*”. In the last phase of the life, cerebral circuits utilize specific strategies which are to be found

in the functional adaptations of the system in order to overcome the “*traps of aging*”. She provides a short list of politicians, scientist, thinkers, who have been very creative till the last days. She started with the architect Michelangelo Buonarroti (1475-1564) and from his *Pietà Rondanini*. Then she discussed Galileo Galilei (1564-1642) and his *Discorsi e Dimostrazioni Matematiche intorno a due nuove Scienze Attenenti alla Meccanica & i Movimenti Locali, pubblicato a Leida, Appresso gli Elsevirii, MDCXXXVIII*. In those days, Galilei was very old and was hosted by Cardinal Piccolomini in the Archbishop Palace of Siena. Subsequent chapters deal with Bertrand Russell I, David Ben Gurion and Pablo Picasso. Russell (1872-1970) at the age of 90 years published the third volume of his autobiography. Ben Gurion (1886- 1973) was a pivotal for the establishment of the State of Israel. Of Pablo Picasso (1871-1973), Levi Montalcini illustrates the painting dated 1971 (*Maternity and Sitting old man*) and concludes that “*Picasso has been the artist who marked our times*”.

She might have added to the list two old men of the Académie Française, Jean Bérard and Jean Guilton ⁵²¹. They were next-door neighbors and they used to meet in the morning and to walk together. Bérard – hematologist of great influence – was ninety-six years old. Guilton, who is considered with Emmanuel Mounier the greatest Catholic philosopher of the Century, was ninety years old. One day Guilton asked “*Why men die?*”. “*Unable to answer* – said Bérard – *I told him about a child who had asked me the same question and to whom I had answered that aging is not desirable. The answer had met child's approval: one should remain fixed always at the same age. Six years*”. Guilton smiled. He wanted to speak of aging and on the remedies to slow it from inception. However, I did not know more than him and just congratulated him for having reached that venerable age keeping the integrity of all mental qualities. It was due in part to heredity, but also to the strict control of the life style. He did not drink alcoholics, did not smoke, adhered strictly to a diet typical of a vegetarian monk, he used to take a few drugs, and did not drive a car. To let him smile I quoted some words of Paul Valéry: “*Mâitre cerveau sur son homme perché*”. He looked at me and assuming a candid attitude asked “*What more?*”? “*The problem of the future of medicine and of the quality of life depends in finding appropriate means to keep the mental balance, to renovate brain cells, as well as those of the other crucial organs. May be they will succeed. However for you and for it will be tremendously late*”.

Rita Levi Montalcini might have added to the list Emile Boutroux. At the age of ninety year the philosopher was moving towards rue d'Ulm for his last academic course, hoping for the last time to be capable to generate new

critical minds, by making this last contribution based on all that had nourished his life. "For me he embodied the wisdom, the wealth of the culture, the astonishment of the beginner" wrote Jean Guitton^{21 22}.

DO EMERITI AND RETIRED PROFESSORS HAVE A REAL ROLE?

Joseph Roth²³ in *Flight without end* mentions a German university along the river Rhine, when the university was forced to nominate a great number of emeriti. The title was a *conditio sine qua non* to be admitted to the local university club. But university professors who participated in our inquiry¹⁻³ were interested in teaching and research. In fact, they do know that "Teaching and research are a continuum, they should not be separated, since as Feynman says teaching is indispensable to generate new ideas and student's questions are crucial to stimulating thinking" (Feynman RP, Are you joking Mr. Feynman?).

It is therefore understandable that at the Second University of Naples professors emeriti "are allowed to teach without specific remuneration. They can study and do research". The constitution reads: "The title may be conferred on those professors who have made illustrious the University with their highly ranked scientific activity as measured by means of bibliometric indices, such as a total Impact Factor and/or H-index higher than the mean of their scientific sector. In addition, emeriti should possess at least one of the following in qualifications: either the presidency of a national or an international society, or the participation of the board of international journals or to have covered the role of president, dean, director of sub-specialty schools, director of the department, member of the academic senate, and/or of the administrative council".

Luc Montagnier, the Nobel Prize for medicine and physiology in 2008 who was forced to retirement, pointed out that "although most advances in physics and mathematics are achieved by the young, in biology many are driven by those with age and experience"²⁴.

Peter L. Berger, emeritus professor of sociology at the Boston University, a scientist who continues to write significant books, recently declared himself to be very proud of his last position of senior research associate. The ambiguous title allows him to continue to coordinate a series of special projects as well as to have a place where he can pause and contemplate grand thoughts by keeping himself in exercise for the last sonata, although this may generate the unpleasant sensation that life is at an end²⁵.

APHORISMS, SAYINGS AND PROVERBS ON AGING

1. Aging is a disease (Terence).
2. More than death one should fear old age (Juvenal).
3. Let cherish and love old age, for it is full of pleasures if one knows how to use it (Seneca).
4. It is old age, rather than death that is to be contrasted with life (Simone de Beauvoir).
5. Old age is life's parody (Simone de Beauvoir).
6. Do not forget that old age is life (Domenico Star-none).
7. Old age is where one shows his personality, it is our most complete essence (James Hillman).
8. The evening is the best part of the day (Ishiguro Kazuo).
9. Age is the premonitory sign of death (Edgar Morin).

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Falling back to experience: retired paediatric professors as a solution to Europe's child health care crisis?

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Background. Human resources of child health care service systems have a major impact on child health. However, there is no formula available to determine the right number of paediatricians with the right age and skill mix in a given country. Several countries in Europe have reported a shortage of paediatricians at a time when general child health care is in crisis for a multitude of reasons.

Aims. To study the role of emeriti professors of paediatrics in children health care.

Results. Our article presents the results of a European survey showing that retired professors tend to play a marginal role in the academic life of university children's hospitals of the majority of 28 representative European countries.

Discussion. This lack of integration contrasts with the potentials of retired professors of paediatrics concerning knowledge and experience in supporting child health care services and in developing strategies for coping with the crisis of child health care.

Key words: Child health, Number of pediatricians, Emeriti professors of pediatricians, Lack of integration, New strategies

INTRODUCTION

Although differences exist in the quality of child health care services in the 53 European countries, it is safe to say that child health care service delivery systems in the majority of European countries are in crisis ¹. This problem could be traced to a number of factors, however, the 2008 economic crisis is indisputably a major contributor. In addition to economic challenges, Europe's child health care crisis is worsened by external factors like climate change and other socio-political global factors, which negatively affect child health in Europe. Despite these circumstances, astonishingly, many opinion makers still act on the principle of "business as usual".

Between 1980 and 2010, mortality rates of children

under 15 years of age in Europe reduced substantially, from 120 to 40 children per 100,000 children ². However, a closer examination of the data paints a more complex picture. As an example, the data reveals that if Germany and the United Kingdom (UK) offered the same kind of health care system as Sweden, 815 German, and 1951 UK children would not have died in 2010.

The list of old and new problems and challenges of child health care service systems is long, and includes many risk factors. Some of which are listed in Tab. I. In our opinion, the problems of child health care are exacerbated by factors like inadequate application of mind-models like the "root-cause-effect-outcome" (Tab. II), and the "lifecycle model" (Tab. III) ³. Social financial investment in the health of children is also inhibited by an

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Tab. I. Barriers and challenges of child health care.

A. Socio-cultural problems of child health care
<i>Health care in general</i>
<i>a. Pathogenetic factors</i>
1. Poverty
2. Lack of health education
3. Lack of safety
<ul style="list-style-type: none"> • E.g. pollution • E.g. traffic • E.g. inadequate nutrition
4. Psychomental threats
<ul style="list-style-type: none"> • E.g. brutalization of media • E.g. drug addiction
5. Children are not in the centre of national interests
6. Child' s rights to health are not listed in national constitutions
<i>b. Missing salutogenic factors</i>
Lack of:
<ul style="list-style-type: none"> • physical activity • music and dance activities • child adequate free time • cultural activities e.g. reading, visits of museums ecc. • child friendly behaviour of adults • stable relations of family members
B. Problems of child health care services
<i>Paediatric care in particular</i>
1. Supply gaps on weekends
2. Supply gaps during night times
3. Fragmentation of child health care
<ul style="list-style-type: none"> • E.g. gap between ambulatory and hospital care • E.g. gap between generalists and specialists
4. Lack of physicians' adherence
<ul style="list-style-type: none"> • E.g. to guidelines and quality standards • E.g. to recommendations on adequate communication with children • E.g. rights of children • E.g. recommendations of participation of children
5. Professional selfishness of different paediatric subspecialties
6. Imbalanced distribution of financial and human resources leading to a lack of:
<ul style="list-style-type: none"> • high tech diagnostics and therapeutics • undersupply and oversupply • lack of paediatricians

Tab. II. An example for the root-cause-effect-outcome-model of child health care.

<p>The root-cause-effect-long-term outcome-model in paediatrics means for example that inadequate postnatal nutrition can be:</p> <p>the root for obesity which causes a metabolic syndrome which can then negatively affect the cardiovascular system and lead to long-term complications such as stroke and heart attack</p>

Tab. III. The lifecycle model of health care.

<p>Many diseases have their roots and causes in the foetal period and early childhood: e.g. poverty, lack of protection and prevention. If these risks are detected early and treated during pregnancy and infancy, then the total of life long cost of the individual for the health care system will be much lower. If undetected and left untreated the long term complications will lead to higher treatment cost. Every EURO invested into children below 2 years of age is well spent and pays out 7 times more after a latency of 40-50 years.</p>

underlying premise that children are the healthiest age group in society. This is taken as justification for comparatively low financial investment in child health care.

This article seeks to answer two questions:

1. Is the older generation of paediatric professors (emeriti) an under-utilized resource that could mitigate the present problems of child health care services in Europe?
2. Could retired paediatric professors thereby serve as a stand by option in countries with a crisis of child health care services? Although this is a connected issue, this article will not discuss the appropriate age, or circumstances under which paediatricians should be obligated to retire ⁴.

The results of our surveys of the European Paediatric Association on child health care in Europe implies that stakeholders seem aware that paediatric care cannot continue to be practiced as it is done today ¹. There seems to be a general consensus among those affected and involved in paediatric care that something must be done about the situation. However, at both the national and regional levels, there remains a lack of consensus on how best to improve the quality of child care. Although the policy slogan, “better medical care for less money” is widely used, in many cases, this merely leads to a “catch 22 situation”, making the slogan more of a description than a clear guide of how to resolve the dilemma. It must also be noted that there have been some major changes in the health systems of many West European countries. Unfortunately these policy changes were unable to address the crisis. In many cases, both in Eastern and Western Europe, investments in child health care went in the wrong direction, leading to wrong changes in many European Countries, particularly in Eastern Europe.

European child care service systems are now faced with a situation in which further delay of implementing changes will worsen the problem of child care in the short term, leading to more serious, society-wide problems over time. We therefore argue for the position

that improvement of child health requires that future increased investments should be channelled through different federal or national ministries (Tab. IV). This will improve the current situation by implementing new types of:

1. **maternal and neonatal care;**
2. **community child health care;**
3. **hospital paediatrics;**
4. **highly specialised paediatric care in national and international centres of competence.**

Due to space limitations, this article will leave some important questions unanswered. For instance, 1. *What are the motivations for more than 200,000 European paediatricians to improve child health care service systems that cater to more than 200 million European children? Isn't the health care service system one of the most change resistant systems in society?* 2. *How well developed is international social responsibility for all children in times of disintegrating European unity?* 3. *Is learning across borders an efficient way of knowledge transfer in child health care?*

KNOWLEDGE, TECHNOLOGY, CARING AND VALUES

Four key elements characterize the essence of child health care and the clinical and scientific interchange among paediatricians. These are, **knowledge, technology, caring and values**. These four elements include a variety of subgroups, and are all usually present in the practice of every area of medicine. However, depending on the circumstances, the nature, quality and mix of these four indicators could vary widely. This chapter will argue that **values** are the most neglected of the four elements.

Effective physician to child communication is a necessary prerequisite for comprehensive paediatric care. The benefits of successful **communication between paediatricians and patient families are well documented**⁵. However, communication between paediatricians, children and young people, differs fundamentally from communication between general practitioners and adults, thus making a specific child communication training an indispensable requirement to the improvement of child care services.

Vaccine refusal and hesitancy is an example of the success-mistrust-paradox, despite high paediatric cure rates, caregivers remain mistrustful of medical practitioners. Retired paediatricians have the advantage of a long career in which they had the opportunity to learn from interacting with children in their care. Their experience and age opens up the possibility for them to take on the role of a trusted physician and a surrogate

Tab. IV. The following national or federal policy makers should be involved in planning and financing child health care programmes.

Ministries
1. of Health
2. of Labour and Social Affairs
3. for Family Affairs
4. of Transportation, Building and Urban Affairs
5. of Education and Science
6. of Food, Agriculture and Consumer Protection
7. of Justice
8. of Finances
9. of Environmental Protection

grandparent for both children and their parents. Retired paediatricians could thereby be able to reverse the tendency of families in medical care to mistrust medical practitioners.

Communication between professional care givers is an equally demanding challenge. The teamwork approach at the end of the 20th century, has proven to be superior to the 19th century approach of an isolated researcher. However, teamwork could become even more efficient if it was designed in such a way as not to hinder team members from having enough time for individual study. Thus, there may be a need for coaching a team of physicians by a relatively independent experienced mentor, supervisor and trainer such as an emeritus who will help finding a balance between conformism and autonomous thinking.

Cooperation has always been an important value and basis of modern science, and the ability of medical colleagues to cooperate is an important determinant of the success of clinical care and research. "Sportive" **competition of experts** ranks among the top motivators in modern medical research. Paediatric scientists want to be the best of the best, at the top. In one word, they want to be the champions. However, deleterious competition is almost inevitably counterproductive. Retired professors are just as ambitious, but because they have already had a successful career, they might be able to mitigate the poisonous, deleterious scientific competition, and in thus creating to a better scientific environment.

Global medical care means provision of information and standardized health care for all. Younger paediatricians are vulnerable to distortions stemming from two directions. Firstly, they tend to be cocooned within the implicit perceptions of their own culture. Secondly, in many cases, they have been taught theories, assumptions, and hypotheses that create barriers between their respective cultures. These two factors create barriers for acquiring cross-border knowledge. Retired

professors have gone through these episodes and should have learned from the past, making them eligible for becoming advisers of younger researchers. By the end of the 20th century, increased global cooperation in paediatric care sought to open up a new chapter of global cooperation and learning in paediatrics. This initiative was mainly driven by personal friendships of leading paediatricians from around the world, who frequently met at international events.

Effective learning depends on active participation rather than passive engagement. Learning medicine is not so much based on abstract intelligence, but more of a healthy “master - apprentice” relation. Who could do this better than a professor emeritus who is able to teach that medicine is both science and art. Retired professors in paediatrics often have a biography of **basic research during their early years in medicine, then a longer phase of translational research and clinical research during their most active years, and public health care research at the end of their career.** A basic three-year common trunk training in general paediatrics followed by two to three years' higher specialty training in a subspecialty was not offered in all European countries¹. As of 2013, there was no European-wide standard definition of training and accreditation for general and academic paediatricians⁶. National guidelines for training in paediatrics showed great, and in many cases, unnecessary and avoidable variations. Where could teaching and training be better performed than in higher specialised paediatric centres of competence, providing excellent research facilities with a high throughput of patients with severe and rare diseases⁶. In many cases, such centres also offer a full range of diagnostic facilities and interdependent specialties and facilities for the treatment of acute and chronic diseases.

Both old and young paediatricians have access to global media, which creates the possibility of the establishment of **systematic knowledge** on child health. However, young paediatricians lack **long term experience** which may limit their **understanding of metaphysical aspects** of the complicated life of patients.

THE NEED TO PROMOTE CHILD HEALTH CARE SERVICES THAT MATCHES THE CHANGING NEEDS OF CHILDREN

It can surely be said that the European academic paediatric community has attained a level of mutual understanding in child health care. What, however, are the common goals of child health care services to be achieved in our lifetimes? What have leading European paediatricians achieved and what do they desire to

achieve for children in the future? What is the weight of the political voice of paediatricians?

Contrary to the situation in the 50 United States of America, the paediatricians of 53 European countries do not yet speak with one voice. Unlike the 66,000 members of the American Academy of Paediatrics, the 200,000 paediatricians in Europe have not established a similar society. It might also be possible to fill this gap by a European Society of retired professors of paediatrics. Such a smaller and more efficient group might have a better chance to fill the gap of promoting national and international social responsibility concerning child health. A group of enthusiastic emeriti is in the process of establishing a European Society of Professors Emeriti which will not only include retired paediatricians but all kinds of still active professors from all over Europe. In the founding declaration it was stated that “We believe that a university professor is called to continue his vocation as an educator, counsellor and researcher for life”⁷. Based on the discussions at the multidisciplinary conference on “The Human Capital of Age”, held on September 16th and 17th 2016 in Naples, Italy⁸, our article argues that – with regards to the European paediatric crisis – the **human capital of age** is an under-utilized resource, which could promote the present problems of child health care services^{9,10} not only in terms of becoming heard by politicians but because emeriti can talk to all people who are in a position to change public opinion on child health.

Scientists in the intercultural field are vulnerable to distortions. Subconsciously, such scientists look at other cultures in a manner conditioned by their own culture. Until now, there has not been an easy way to transcribe national behaviour from one culture to another. There is no better way for paediatricians to understand cultural differences than studying and working abroad. Most retired professors have spent parts of their career in foreign countries. Assuming unlimited financial resources of countries, the emeritus knows well that national goals might not be the same, because countries sometimes have different priorities. Retired professors could be able to transfer their knowledge and experience to younger people in a team, leading to improved international communication and cooperation. In a competitive medical world, there is also need for competent experts who support a culture of consensus. Such a consensus culture should be based on good clinical leadership and governance, shared values, common protocols, and last but not least, clear decision making processes. In general, it is thought that young people are more flexible in life than old people, which is a factor that could facilitate changes in the medical world. When one

of the authors was teaching career seminars to advanced students and young physicians, he observed that young physicians suffered from a considerable indecisiveness when planning their own career or when establishing their own views and ideals on health care service systems. In Germany for instance, there is a need to stimulate those young people who seem to lack initiative and a trial and error attitude, who thereby favour strategies of pain prevention.

Creativity means bringing up novel ideas during an incubation process of thinking (sometimes unconscious thoughts). Autonomy and non-conformism are prerequisites of creativity. Creativity is only the first step of a process of inspiration which should be followed by activities of teams of people, then productivity and later on by changes in the world. Do retired professor have less curiosity, intuition and creativity than young ones? How could this be measured? Is autonomy age dependent? Financial autonomy is probably more often found in the group of emeriti than in younger paediatricians.

In the course of his or her career, a paediatrician, there may be an influence of age on the productive stages. However, as history shows, the age of a scientist is not a criterion for assessing the value of valuing medical discoveries. As Aristotle says, *“He who sees things from the beginning will have the best view”*. Thus, there is certainly an influence of experience on deciding upon priorities (to do the right thing at the right time at the right place for the right people with the right methods). During the decision making process the cognitive dissonance – which means a gap between conviction (I wish) and actions (I can) – must be taken into account, and the elderly generation may have developed a kind of wisdom or the obligation to be wise. More specifically this could mean that emeriti should aim at developing less passion, fewer emotions, less desire, fewer wishes for themselves. Elderly people are the off-springs of their past. Experience and the use of the philosophical model of deconstruction will encourage emeriti to test the opposite extremes of conflicts e.g. young and old. Deconstruction means searching for the common of young and old that is detectable and positive for and in both age groups.

All these questions will arise in a situation when an emeritus will become an important member of a team of scientists and paediatricians, thus creating a cultural and scientific “parabiosis”. This metaphor parabiosis defines as a special symbiosis, in which two or more people occupy the same professional “nest site” combing the “fountain of youth” with the “source of age”.

WHAT ARE THE PITFALLS OF OUR CONCEPT OF PROPOSING RETIRED PAEDIATRIC PROFESSORS AS A STAND BY OPTION IN COUNTRIES THAT FACE A CRISIS OF HEALTH CARE SERVICES?

A professor emeritus of paediatrics usually ends her/his career as head of department. Becoming the number one of a ranking list means that power (**the desire to be important**), and intellect (**the desire to stay informed and creative**) – in many cases a mixture of both – had been a feature of his career in the past. It is not unusual that some individual characters have a gap between power and intellect, the degree of which is usually influenced by culture and politics. In our opinion, it would certainly not be a good idea to ask a power-seeking emeritus to continue her/his clinical work as a senior professor in the routine clinical services within hospital because she/he may block the career of young shooting stars in the team.

There could also be reasons why retired paediatricians may not be interested or able to continue working on a voluntary and honorary basis e.g. as an active emeritus who is not adequately paid for his/her work. Some of these reasons could be health problems, loss of skills, family issues, burnout and other psychological issues ecc. We should therefore not be taken to be advocating for the compulsory retention of retired professors. Retired professors should not be pressured into continuing to practice. The choice must be made on a voluntary basis.

WHAT ARE THE LEGAL HURDLES TO CHANGE THE CURRENT ROLE OF EMERITI IN EUROPE?

In many European countries, an employer can legally force a professor of paediatrics to retire at a certain age. To the best of our knowledge, no European country has in place, the equivalent to the US-American Older Workers Benefit Protection Act (OWBPA 1987). This is a law which states that you cannot be fired on account of age.

Since the legal conditions of retirement are heterogeneous in Europe, we are describing “pars pro toto”, the current situation in Germany. Germany seeks to become a country that is characterized by a non-discriminatory culture. The new General Act on Equal Treatment (Allgemeines Gleichbehandlungsgesetz, AGG) of August 1, 2006 ensured equal treatment for all in the workplace. As a result, employers are now expressly prohibited from discriminating against job applicants or employees on the basis of gender, race or ethnic origin;

religious belief; disability; or sexual orientation, and age. To achieve the goal of becoming a no-discriminatory culture, Germany will have to be more aggressive in the incorporation of measures against discrimination into society to a larger extent than it currently does. There must no longer be different treatment between old and young persons. The current laws now require that the same level of protection be made available to both old and young persons. There are however specific exceptions in German law with regard to retirement. In Germany, the legal retirement age was recently raised from 65 to 67 (for individuals born 1964 or later). Therefore, an employee can be forced to retire upon reaching the retirement age. In some Federal States of Germany, a different legal retirement age applies for **civil servants**, i.e., retirement of professors may be deferred until the age of 68.

SURVEY ON THE ROLE OF RETIRED PROFESSORS OF PAEDIATRICS IN EUROPE

How would the idea of the empowerment of retired paediatric professors fit into the youth obsessed culture of the Western world? Should these old paediatricians fill the gap that arises from a lack of newly trained paediatric subspecialists? ¹¹. Where should a retired professor have her/his office? Should a senior professor get a salary in addition to her or his pension? The improvement of health care systems requires first to clarify the current status, then to answer the question, "What will happen in the future?" and finally, to define the urgency of the concern in order to eliminate deficits. Unfortunately, data on the current role of retired paediatric professors in European countries was lacking. With these thoughts in mind, the European Paediatric Association studied the role of retired professors of paediatrics in 2016 in 28 European countries. These were made up of 18 of the 28 European Union countries; 8 East European countries, including Russia and Turkey, plus Israel and Switzerland. The questionnaires were answered mainly by presidents of national paediatric societies. In the Mini-Questionnaire we were asking mainly for estimated data on the role of retired professors, because no country had official statistical data on their activities. The results of the analysis on rights and duties of an emeritus are very heterogeneous from country to country; and within countries, from university to university. 24 of 28 countries had fixed ages for retirement (10 countries at 65 years of age, 7 at 67 or 68 years, 7 at 70 years). Four countries had a flexible age limit with the option for females to stop working at the earliest at 55 yrs and for males at 60 years. Five of 28 countries did not establish the status of emeritus in their university

constitutions. 10 countries had written rules for selecting an emeritus, 8 did not, and 10 presidents did not know.

The extracted rights and duties of emeritus professors in paediatrics are listed in Tab. V. These results have led us to believe that the emeriti were not well integrated into the academic live of half of the 28 European countries studied. This assumption is supported by the results that less than 5% of retired professor were active in clinical care, research and teaching, in 6 countries. In 6 countries, Presidents of national paediatric societies were not informed about the rights and duties of an emeritus. There was a trend that retired professors were more often involved in postgraduate, rather than undergraduate teaching. Thirteen of 28 countries reported that a wide range of 10-80% of retired professors were still active in research. Of the 28 countries studied, 11 countries reported that retired professors were still active in clinical care.

CONCLUSIONS

Our findings of the survey show that retired professors tend to play a marginal role in the academic life of university children's hospitals of the majority of 28 representative European countries. This lack of integration contrasts with the potentials of retired professors of paediatrics concerning knowledge and experience in supporting child health care services and in developing strategies for coping with the crisis of child health care.

Tab. V. Selection of rights and duties of emeritus professors in paediatrics which were reported by presidents of national paediatric societies in Europe.

A. Rights
1. Office (e.g. shared with another emeritus) plus personal computer and internet access, free telephone line), secretarial support.
2. Free parking
3. Support for application of research grants
4. Laboratory bench in case of own research project (renewable contracts according to external funding)
5. Cooperation with research fellows
6. Regular information on local conferences and grand rounds
7. Extra salary
B. Duties
1. Mentoring, teaching and training of students, young paediatricians and research fellows
2. Consultants to hospital business and advisors in leadership and good governance
3. Liaison officer with international paediatric societies
4. Liaison officer with editorial boards of paediatric journals
5. Ombudsman

In cases where the rules no longer match the reality, it is usually easier to change the rules first, in order to bring the reality closer to the ideal. We therefore conclude that medical organizations in Europe should discuss career pathways for senior academic paediatricians¹² and subsequently the Council of Europe and the European Commission should start an initiative on empowering emeriti in paediatrics in Europe to act as promoters for the well-being of children.

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REVIEW

The ideas of Plato, Aristotle, Plutarch and Galen on the elderly

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For the sake of brevity, we will deal here with a very small fraction of the texts of ancient Greek writers on Old Age, in a period of roughly 600 years between the 5th century BC and the 2nd century AD. And geographically also, the area covered is but a negligent fraction of the globe.

Aim. To comment on a very small fraction of the texts of ancient Greek writers on Old Age, in a period of roughly 600 years between the 5th century BC and the 2nd century AD.

Materials and methods. We used extracts from the writings of Plato (*The Republic*), Aristotle (*De Anima*), Plutarch (*Vitae Parallelae, Moralia*) and Galen (*De Marcore Liber*).

Results. Plato presents two sides of the stance of elderly, i.e. continuity (to continue to do what they were doing in their active years), and disengagement (describes the tendency after some age to go away from your previous straggles and to contemplate on the eternal values of spirituality). Aristotle explains why in old age death is painless, like the shutting out of a tiny feeble flame. Plutarch elaborates extensively on the need to accumulate physical and mental qualifications when we are young so that we can be able to consume them later, in our old age. He declares that “*although old age has much to be shameful of, at least let us not to add the disgrace of wickedness*”. Finally, the social role of each person shall not mutate with age. Even bees do not become drones when they age. Galen supports the view that ageing is inevitable, although this is only confirmed by experience and not by science.

Conclusions. According to the cited authors it could be said that it is the cordial acceptance by elders of the limitations of age the term that will ensure their cordial acceptance by individuals of all ages living in society.

Key words: Elderly, Plato, Aristotle, Plutarch, Galen

INTRODUCTION

Let's start with two Greek poems, one modern and one ancient to give the stigma of my contribution which embodies the aphorism “*It is not how old you are, it is how you are old*”¹. These two poems in juxtaposition parallel the two Janus' like faces of Old Age.

The first poem is:

The Souls of Old Men

Inside their worn, tattered bodies

dwell the souls of old men.

How unhappy the poor things are

and how bored by the pathetic life they live.

How they tremble for fear of losing that life, and how much they love it, those befuddled and contradictory souls, sitting – half comic and half tragic –

inside their old, threadbare skins

written by Constantinos Kavafys at the first half of the 20th century².

And the second one is the final comments by Chorus in the tragedy “*Antigone*”³: “*The most important thing in*

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man's happiness is good judgement and he must not treat with disdain the works of the gods. The arrogant pay for their big proud words with great downfalls and it is only then, in their old age that they gain wisdom!", written by Sophocles in the 5th century AD.

Having used manifolds the term Old Age, let us define when does it start? Again, the boundaries are unclear. The results of limited research shows that the average lifespan in Classical Greece was about 25 years, if assuming the date of birth as a benchmark, but increased to up to about 42 years after adulthood, due to high infant mortality⁴. In the Roman period, it was calculated at 72 years⁵. It follows therefore that, in the society during the period under review, the old were younger and fewer than in our own era, and there were many young people to care for them. To document my thesis, I have chosen extracts from the writings of three famous philosophers (Plato, Aristotle, Plutarch) and a famous doctor (Galen) as representatives of how this society was viewing the elderly. The choice of the extracts tried to compromise the twin impulses of the historian, to archive and to narrate, which are often in tension. The archivist wants to collect and preserve, indiscriminately and exhaustively, the artifacts of history. The narrator, by contrast, seeks to tell a story by emphasizing certain of those artifacts at the expense of others, judging, at least implicitly, which of them are significant and which are not⁶. Let us start with the ideas of Plato, presenting some small excerpts of his work *Politeia (The Republic)*, related to old age. In brief, Plato hints on the two different stances of aging. The continuity and the disengagement. With continuity he recalls the strife of some elders to continue to do what they were doing in their active years both as a means for staying robust and also for insisting that their previous efforts were not spent in vain. With disengagement he describes the tendency after some age to go away from your previous struggles, goals, achievements and to contemplate on the eternal values of spirituality⁷. He tries to compromise both stances in his famous description of The Escape and the Return of the Wise Old Man to the Cave^{8,9}. There, in an imaginary prison, were kept captured the minds of the many chain-bound from the superstitions and the conformities of the society. After ages of struggling the Old Man manages to escape in the pure light of the Wisdom. He is free from all conventions and ambitions. Just as the Emeriti Professors should be. And then Plato wonders if it is permitted to leave them there to contemplate. He decides that even against their inner will, as a public duty they should return back to the Cave as mentors to liberate the *hoi polloi* from the conventions and the social lies. Exactly as the Association of the Emeriti promises to do.

The role of the elderly as advisers was an accepted duty

in the Greek World as far as the Far East as documented an inscription on a Herôon in Afghanistan (<https://vi.scribd.com/.../Ai-Khanoum>). But let us be aware. We should not over-advise the younger provoking their anger. This was successfully expressed in a prayer by an unknown abbess in the 17th century "*Lord, thou knowest better than myself that I am growing older and will soon be old. [...] Keep me from becoming too talkative, and especially from the unfortunate habit of thinking that I must say something on every subject and at every opportunity. Release me from the idea that I must straighten out other peoples' affairs. With my immense treasure of experience and wisdom, it seems a pity not to let everybody partake of it. But thou knowest, Lord, that in the end I will need a few friends. Keep me reasonably gentle. I do not have the ambition to become a saint – it is so hard to live with some of them – but a harsh old person is one of the devil's masterpieces*"¹⁰. Plato then recalls Socrates view that wisdom is really is the "Knowing you do not know" and not gained before the age of 50. Similarly, Aeschines tells us that in the early democracy (before the 5th century) citizens over 50 years of age could speak first, and only after those had their say could younger men speak¹¹. However, according to a humane instruction by Plato the elderly should not be restricted in a life of everlasting sobriety. Because "*as iron became softer by fire old men become softer by wine – which they are allowed to drink more than the youths – and are not ashamed to sing in the company of friends, thus regaining their youth. Also they can speak about their experience while when somber they were embarrassed to do so. The young will also gain having the opportunity to listen to all*"¹². This merry old age cannot last for ever. In another passage, he makes an original parallelism: "*And old age gradually comes. And then we should quickly surrender, as in debt to life. Because if we delay this, Nature, like a debt collector, will pledge our vision, or hearing, or even both. And if he persists in delaying the payment of his debt and to continue living, she sends paralysis and senility. Until the gods take pity on him and relieve him with death*"¹³. Finally, he backs my initial statement by a discussion with his teacher: "*But I tell you Socrates; here there are gathered many who have about the same age as us. And they begin to complaining and feeling resentment because their old age has deprived them of women, drinking and fun. And they have aches and those around them laugh at them. And for all this, they blame old age. But I think they found the wrong reasons. Because if ageing was the cause, you and I should suffer from the same, given that we are now old. But yet we are happy. And I found Sophocles and asked him how he was getting on with women. He told me he is happy, as he is now relieved of the venerable*"

passions that tormented him during his youth. Thus, I believe it is not old age, but character that is responsible. If you were a good and meek youth, you will have a good old age; if you were shrewish you will be an unhappy old man"¹⁴.

The second philosopher is his disciple, Aristotle. He makes a very clear distinction between the two modes of death similar to the two modes a fire is extinguished. Either from an external cause, and he calls it by extinction, or by just old age, the latter called by exhaustion. He elaborates further his parallelism explaining why in old age death is painless, like the shutting out of a tiny feeble flame. In an excerpt, he presages contemporary corneal transplants: "*If an old man received the eyes of a youth, he would see well. Because his soul and spirit are not damaged but only his sensory organs, as in disease and drunkenness, but the cause of this inability to sense is internal, while the spirit and soul remain unaffected*"¹⁵. More succinctly, he notes "*Illnesses are the companions of old age*".

Proceeding to the commentary on the second historical unit, the 1st century AD, I have chosen to present some relevant excerpts from the oeuvre of a profound author of Late Antiquity, Plutarch. Repeating Plato's writings more eloquently, he tells us that the essential element for ensuring a good old age is a good youth. Apart from this common-sense remark, Plutarch notes that we should accumulate physical and mental qualifications when we are young so that we can be able to consume them later, in our old age. From the same viewpoint, he expresses the view that a happy, joyful and soulful character radiates so much inner pleasure that it will protect us against the self-pity of old age. A virtuoso on similes, he parallels this internal radiation with internal body heat. He correctly observes that it is this internal radiation that keeps people warm and not their various garments, which by their nature are thermally neutral, and contrary to what many people think, not heat them, but simply prevent the loss of their internal heat. Just like a lovely perfume will make even the poorest rags smell fragrant, while a septic stink will make even the most luxurious garments stink, our innate hilarity will allow us to avoid the sorrows of old age¹⁶. He comments on the malice that nests in the soul of man, like a wicked wife who poisons the soul of even socially successful people when they return to their home. Innate malice is actually even worse, as you can get a divorce from your wife, but not from the evil in your nature. In the end, his cry that "*although old age has much to be shameful of, at least let us not to add the disgrace of wickedness to be expected*"¹⁷. He concludes this series of reflections by saying that if you follow his advice and reach such an old age, then, without scorning any of the joys of life, you will not be their slave. You will rejoice in wealth as it

will give you the opportunity to be beneficent but also in poverty, since you will live a carefree life, without having to care for property. You will enjoy state offices, but will feel equally happy leading a private life. Plutarch begins with the main argument that the human mind is an organ that not only does not become useless over time, but improves, thanks to the wisdom of experience that is continuously added. The only thing that even war, which sweeps over everything like a torrent, cannot destroy is education. On the contrary, we ought to even amend the saying of Pericles, in his great oration over the Athenians who fell in war, that "*The love of honour alone never grows old, and in the useless time of old age the greatest pleasure is not, as some say, in gaining money, but in being honoured*" because that the same is even truer of the spirit of service to the community and the State, which persists to the end. He recalls that Simonides in his old age won prizes with his choruses, as the inscription in its last lines declares: "*but for his skill with the chorus great glory Simonides followed, Octogenarian child sprung from Leoprepes [his father's] seed*"¹⁸.

Finally, the social role of each person shall not mutate with age. Even bees do not become drones when they age¹⁹. Unlike some elderly politicians, who demand to sit at home inactive while taken care of by the state. There is no worse sin, he says, according to Cato, from a prominent politician withdrawing due to age and staying at home having fun with women's work or playing the farmer. Withdrawal from every sector of active participation is the worst attitude for the mental health of patients, one of the factors leading to depression, which is a predisposing factor for malignancies, and a safe way for those around you and society to get bored with you and avoid spending money, time and effort to treat you. This decline is paralleled with the fate of Paleros, the sacred vessel of the Athenians, which, after a brilliant career, ended up with its wood being used for kindling and small tools by anyone who came by. Let it not be thought that the crown of old glory is like the wreath of dried flowers on the head of old athletes. It needs some care to always stay fresh. Thus, former glories need some new activity to be renewed. Like the small wooden parts that maintainers use to replace rotten parts in the Delian ship so that it can always remain in good condition. Likewise, the elderly will always retain their glory, even if they offer just a few useful things to society. Since an old friend does not constantly need great gifts, but maintains his friendship through little reminders, like a smouldering fire that just needs some prodding to be kept alive¹⁹.

Having finished the presentation of a few excerpts from the works of Plutarch, I proceed to the most prolific medical writer of antiquity (and all time), Galen. In line

with these previous authors, he supports the view that ageing is inevitable, although this is only confirmed by experience and not by science²⁰, and mocks those who propose elixirs to combat it, saying “*It is said that ageing is inevitable. But a philosopher wrote a book when he was 40 years old, in which he provided advice on how to never get old. He lived until 80 years old, shriveled, with a pointed nose, twisted ears and sunken eyes. Everybody taunted with about how he used to tell others not to grow old, but he himself became very old. He later published a second edition of the book, which he called the “miraculous agelessness”. In this, he supported that, to avoid getting old, humans need a certain physique, as well as a certain diet. And he undertook to raise children from infancy onwards with these diets, so that they would never grow old. However, he died before the children grew up so no one could check the accuracy of his statements”*. Copying Plato and Plutarch, Galen noted “*Solon too took the view that ageing requires much care. Not only food and clothing, but also a warm home and amenities. It is like a harsh winter. Like a good governor, who supplies the city with goods for the winter in good time, man should accumulate all that is necessary from his youth, for when he gets old”*”.

I will try to summarize now how these teachings of the ancient philosophers and physicians are useful for the behavior of the younger towards the elderly. Apart from the respect that is somehow required by the younger, it should be understood that the continued inclusion of elders in social affairs is also actually to their advantage. Their experience and the lack of overenthusiastic reactions will prove equally beneficial with their own courage. But they also benefit selfishly, since they will inevitably reach the position of these elders at some point and a society that has learned to respect the elderly will treat them well too. However, the greatest value of the ancients' thoughts lies in the acceptance of ageing as a normal progression of life without the current frenzy about its abolishment at all costs. And also in the analysis of the responsibility of the elderly themselves. They cannot demand respect and acceptance simply because they have grown old. Only a pension is awarded *ipso facto*, although even this is disputed today! They cannot argue that the greatest achievement of their lives is that they did not die earlier and are therefore entitled to primacy. A proper life, from youth onwards, endows the individual with the necessary reserves for old age. And only if the years gone by have provided the expected wisdom does the demand for participation of the elderly in their excessive healthcare costs justified. In conclusion, it could be said that it is

the cordial acceptance by elders of the limitations of age the term that will ensure their cordial acceptance by individuals of all ages living in society.

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