WP1: Methodological framework to evaluate clinical and functional status in age-related diseases, multimorbidity and frailty

Focus on designing and implementing educational programs on ageing (Ph.D. Ageing School: Pathophysiology of and prevention of frailty and disability among older adults – AgingPath)

Objective (six mounths): Design of a new PhD programme AgingPath

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PhD Aging School: Pathophysiology of aging and prevention of frailty and disability in elderly subjects (AgingPath)

Epidemiological, cultural and scientific scenario

We have been witnessing a constant aging of the Italian population, like that of other Western countries and recently also of emerging countries. This demographic trend makes Italy one of the oldest countries in the world. With the increase in the elderly population we observe an increased risk of developing disabilities, cognitive impairment and chronic diseases, conditions which have a great impact on the cost-effectiveness of social and healthcare services.
Aging is not a homogeneous process. There are elderly subjects whose aging can be defined as successful (the so-called "successful aging") characterized both by the absence of significant chronic diseases and by a level of health perceived as satisfactory and by the presence of self-sufficiency with satisfactory capacity for temporal orientation. space. In other elderly people, it is possible to observe the decline of numerous functions of organs and systems associated with the presence of at least two chronic diseases, representing the so-called "usual aging". Aging is characterized by the loss of self-sufficiency, a serious reduction in cognitive abilities and the presence of numerous chronic-degenerative diseases ("catastrophic aging") which rapidly leads to that condition of fragility that characterizes the elderly population segment. weaker and at risk of institutionalization.

From an epidemiological point of view, one of the characteristics of the elderly patient is the presence of comorbidity (understood as the coexistence of 2 or more diseases in the same subject) in direct correlation with the increase in frequency of chronic-degenerative diseases with age. This peculiarity significantly influences the approach to the elderly patient both in terms of clinical presentation (making the interpretation of symptoms and signs more complex) and in terms of pharmacological treatment in consideration of the need to use drugs for a particular disease which, on the pharmacokinetic and pharmacodynamic, may not be compatible due to the co-presence of another pathology. Furthermore, the phenomenon of comorbidity has in fact represented a reason for the exclusion of geriatric patients from large intervention and prevention trials, significantly reducing the possibility of geriatrics to transfer "tout court" the results of evidence-based medicine into clinical practice. There is ample evidence that the pathologies with the highest prevalence are represented by arterial hypertension, followed by osteoarticular pathology and chronic obstructive pulmonary disease. Diabetes, heart failure and the co-presence of multiple chronic diseases are the most important prognostic markers of mortality. In particular, the interaction of all the pathologies increases the risk of mortality at 12 years by approximately 16 times, unequivocally demonstrating how comorbidity represents a prognostic factor determining mortality in the elderly subject. Furthermore, comorbidity has an important impact on disability. It should be remembered that disability has and will

have an enormous impact on the organization of health and social services, having to favor not only integrated models of assistance where multiple professional figures work interacting with each other, but also models of assistance networks ranging from structures traditional care (hospital, day hospital, clinic) to non-hospital facilities (home, care homes for the elderly and day centers).

The unfavorable socio-economic context, the absence of an efficient network of community health and social services are all strong predictors of new hospital admissions and mortality in the elderly population. It should be noted that several studies have demonstrated the role of social support on morbidity and mortality and demonstrate a lower death rate for older people with a higher degree of social support. This relationship is confirmed even when focusing on mortality due to cancer, coronary heart disease and all cardiovascular diseases

Although there is no universally recognized definition, frailty is considered a clinical condition that occurs when the state of "vulnerability", intimately linked to the age-related decline of the functional reserves of the elderly subject, is assisted by the intervention of "external stress", for example, a re-acutization of a chronic-degenerative pathology, to a compromise of the four domains determining the global state of health: physical, mental, nutritional and socio-economic.
Initially, in 2001 frailty was identified with the "Frailty phenotype" according to Fried et al. This index focuses on “physical frailty”, identifying frailty with the presence of three or more deficits including: weight loss, fatigability, weakness, slowing down in walking and reduction of muscular strength. Therefore, initially frailty was recognized only in the "physical" domain, but subsequently frailty was identified in a more complex “multidimensional” model which also includes the evaluation of the psycho-cognitive, nutritional and socio-economic aspects. According to this approach, in 2007 the most used tool for assessing frailty is the "Frailty Index" (FI) of the Canadian school, expressed as the ratio between the deficits found in a subject (physical disorders, cognitive, nutritional and psychosocial risk factors) and the total number of deficits investigated proposed by Rockwood and Mitnitski. This instrument was validated in the Italian language first in its extended form (40 items) in 2017 by Abete et al. and subsequently (2020) in a short version (Fr-agile, 10 items) by Liguori.

The interactions between biology, clinics, socio-cultural changes and environment make the aging process a particularly complex process and for these reasons it is mandatory to promote professional, cultural and research training processes in order to create that critical mass of professionals and researchers for age-related challenges.

Introduction

In order to develop the PhD Program in Pathophysiology of aging and prevention of frailty and disability in elderly subjects (AgingPath),

- **a)** we organized 2 meetings to decide the main methods that our students will have to acquire to allow the development of translational skills. In particular**, the main methods of evaluation of biological markers and the implementation of relational skills to fully dialogue between graduates of different and complementary disciplines.**
- **b)** we organized a series of seminars to develop the geriatric-gerontological culture in our PhD students who are attending the "Cardiovascular and Gerontological" curriculum already present in the PhD Program in Experimental Clinical Medicine at Federico II University of Naples. **These seminars have the aim to verify whether there is a feeling and interest among PhD students in developing themes relating to the pathophysiology of aging and prevention of frailty and disability.**
- **c)** we have planned deepen knowledge of the scientific literature on the involvement of follicular T-helper (TFH) cells in the aging process. The aims are to study the modifications of this cell type by cytoflorimetry on immune cells, which we expect to have a pattern specific to aging. At the same time, we have identified a series of biomarkers that will be validated and evaluated in the populations of interest of the project. In particular, the expression levels of these biomarkers will be related to the various degrees of frailty. During this period, we have developed the methods to be used. **These methods will be one of the most important skills to acquire during by PhD Program in Pathophysiology of aging and prevention of frailty and disability in elderly subjects.**

The aims of a PhD Aging Path

The PhD Aging School: Pathophysiology of aging and prevention of frailty and disability in elderly subjects (AgingPath) has the main aim of improving knowledge of the pathophysiological mechanisms linked to aging and of the main age-related diseases by developing high skills in research in the gerontological field translational, clinical and socio-epidemiological.

In particular, the PhD Aging path aims to develop high-profile skills relating to the molecular and pathophysiological bases of diseases of the elderly with reference to the pathophysiological aspects, the new diagnostic-therapeutic perspectives of diseases of geriatric interest including heart failure, senile dementia and chronic-degenerative diseases.

Part of the course will also be dedicated to the epidemiology of chronic non-communicable diseases related to ageing, the clinical approach to them and their economic and social impact.

The participation of doctoral students in cultural initiatives, meetings, conferences and workshops at national and international level is expected. Doctoral students will be encouraged to publish the results of their research as abstracts, manuscripts and publications in peer-reviewed journals. For doctoral students, a mandatory training activity of at least 12 months is envisaged at a non-Italian academic or research institution also in order to promote the internationalization of the PhD Program.

The main aim of the PhD Program in Pathophysiology of aging and prevention of frailty and disability in elderly subjects will be to promote training and research in the emerging fields of the pathophysiology of aging, the early identification of age-related diseases such as heart failure and dementia and in the prevention of functional changes related to aging and the main age-related chronic degenerative diseases.
To achieve this aim, the training activities will be carried out at Italian and foreign centers of excellence with documented expertise in the field of aging, promoting the integration between translational research and clinical practice.

The training activity

The training course lasts 3 years and is achieved with the achievement of 180 Educational University Credits ((EUC in Italian CFU): 60 EUC per year. One EUC corresponds to about 25 hours of training activity, divided into time for webinars, lectures and advanced training courses and time for independent study and/or research by the doctoral student.

The training activity of the PhD Aging School: Pathophysiology of aging and prevention of frailty and disability in elderly subjects (AgingPath) will consist of: Advanced training courses, Webinars, small group lessons, research-related activities, training and research activities chosen independently by the doctoral student and approved by the Doctoral School Council

The training activities of the program The PhD Aging School: Pathophysiology of aging and prevention of frailty and disability in elderly subjects (AgingPath) will focus on 5 main areas of interest:

a) Heart failure and biomarkers;
b) Dementia and neurodegenerative diseases;
c) Chronic degenerative pathologies of geriatric interest (Hypertension, Diabetes, Osteoporosis, etc);
d) Health Aging;
e) Non-pharmacological prevention of the negative effects of aging on cognitive and physical performance.

The planned training activities will be both theoretical, methodological and experimental, in the field of aging and age-related pathologies. A transversal approach

will be favored with other medical and non-medical disciplines (biotechnology, statistics, engineering, sociology, etc.) with the aim of developing the following skills:

a) to know and to be able to use the main basic and clinical research tools aimed at investigating the mechanisms of aging and the progression of age-related chronic diseases, including biomarkers and models for the prevention and treatment of frailty and disability;
b) to be able to conceive, plan and carry out a research project;
c) to develop the necessary skills of synthesis and evaluation of possible complex issues related to research or innovation projects and how to overcome them with particular reference to the ability to interact with experts from other disciplines;
d) to be able to use the available knowledge in order to improve both the basic and pathophysiological knowledge of aging and the main chronic diseases and the pharmacological and non-pharmacological approaches for the prevention of the negative effects of aging on performance and the main age-related diseases by proposing innovative approaches and alternative care models.

The 3 years of the PhD course

The PhD course will develop over 3 years and will be organized as follows:

First year
The doctoral student will choose, together with his tutors, the main research theme or themes that will be developed over the 3 years. The training activities will take place, as planned, in the form of webinars, frontal lessons and small group lessons and advanced training courses specific to the chosen curriculum, as well as with activities related to research.

Second year
The doctoral student will consolidate his research activity by carrying out research programs both in the home structure and in Italian and non-Italian locations.

Third year
The doctoral student will be encouraged to finalize their research through the publication of the results and will dedicate adequate time to the preparation of the final thesis.

During all three years the PhD program will include a series of advanced training courses such as a) basic and advanced statistics aimed at both the evaluation and implementation of experimental, clinical and epidemiological studies; b) study of the English language; c) design and management of clinical or translational studies.

Doctoral students will be required and encouraged to dedicate adequate time to the preparation of the webminars also through the critical evaluation of the literature available on the topics encouraging the doctoral student's development of critical thinking and stimulating debate and interaction with the teaching staff and the other students.

Doctoral students will be encouraged to participate in national and international workshops, conferences and congresses as speakers, as well as being involved in collaborative research projects aimed at the scientific growth of the doctoral student with research groups and laboratories external to the doctoral facilities. Doctoral students will be stimulated to present the results of their research at conferences in the form of abstracts and oral presentations.

For their training, limited involvement in integrated teaching activities during the Master's Degrees and in clinical activities consistent with the scientific objectives of the PhD program is expected

The evaluation of the research activities of the individual doctorate is based on the following criteria: a) scientific relevance and diffusion within the international scientific community of each publication produced in peer-reviewed journals of international importance; b) evaluation of the candidate's individual contribution to collaborative work; c) use of bibliometric indicators such as the number of citations received by individual publications, the "impact factor" of scientific journal and overall indicators such as the Hirsch Index.

The training venues of the PhD Program training network must necessarily be characterized by: a) scientific excellence of their research groups; b) cutting-edge centralized structures with innovative technological equipment; c) strong connection with clinical practice; d) strong international vocation; e) excellent scientific publications evaluated according to the highest international standards

Thematic Research Areas

In accordance with the guidelines promoted by the Italian Ministry of University and Research (MUR), the thematic research areas of the PhD Program will be identified with the scientific disciplinary sectors of the members of the Teaching Committee:

BIO/14 – PHARMACOLOGY
MED/01 MEDICAL STATISTICS
MED/03 MEDICAL GENETICS
MED/04 - GENERAL PATHOLOGY
MED/09 - INTERNAL MEDICINE
MED/11 - CARDIOVASCULAR DISEASES
MED/13 – ENDOCRINOLOGY

MED/26 - NEUROLOGY
MED/28 - DENTAL DISEASES
MED/34 – PHYSICAL AND REHABILITATION MEDICINE
MED/42 – GENERAL AND APPLIED HYGIENE
MED/50 – APPLIED MEDICAL TECHINICAL SCIENCES
M-EDF/01 - METHODS AND TEACHING OF MOTOR ACTIVITIES
M-PSI/08 – CLINICAL PSYCHOLOGY
ING-INF/04 - AUTOMATIC
SPS/08 - SOCIOLOGY OF CULTURAL AND COMMUNICATIVE PROCESSES

PhD thesis and admission to the final examination

The thesis of PhD Program Pathophysiology of aging and prevention of frailty and disability in elderly subjects (AgingPath) e will be written in English and must be accompanied by an abstract in both English and Italian. The Teaching Council of the PhD Program will formulate an evaluation of the thesis, the activities carried out during the course and the publications for each doctoral student. The doctoral student must present a report on the activities carried out during the doctoral course certified by the main tutor and the course coordinator. This report must be evaluated by 2 researchers ("evaluators") external to the doctoral course who will formulate an independent written evaluation of the thesis, approving the final discussion of the thesis or proposing further additions or corrections to the thesis. The delay in the final defense of the thesis cannot exceed six months.
At the end of the discussion of the thesis, the examination commission can approve or reject it with a collegial written judgement. The examining commission expresses an in-depth evaluation of the doctoral student with the following grades: sufficient, good, excellent. The examining commission can unanimously award the doctoral student "cum laudae" in case of scientific excellence of the results achieved.

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