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Mini Review

Integrating functional ageing into daily clinical practice

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Abstract

The analysis of the ageing trajectory clearly demonstrates the constant involvement of functional ability in daily life, from its development in youth, to its preservation through midlife into very old age. While maintaining function appears to be largely related to persistent regular exercise, the risk factors for functional decline are extremely diverse, ranging from a decrease or discontinuation of physical activity, to nutritional/metabolic disturbances, chronic diseases and unfavourable socio-demographic and socio-economic contexts. Prevention of functional decline is a major public health challenge, both for individuals and for society as a whole, and needs to be urgently addressed. Engaging citizens to be conscious of their responsibility for, and role in their own ageing process is equally as important as reinforcing the involvement of society in promoting healthy ageing through enhanced basic and health education, promotion of a healthy diet, long term practice of moderate physical activity, and the continual battle against deleterious life habits and behaviours. The success of these combined actions would be quite simply demonstrated by a change from the current pandemics of morbidity, to the compression of disability, which is expected by all.

Keywords: Ageing, Daily functioning, Chronic diseases, Disability, Prevention

Introduction

The European health landscape is gradually adjusting to the challenges posed by the demographic transition. Longevity is increasing steadily, albeit at a slower pace than in the past half century, and fertility rates are at historically low levels. These factors combine to explain that today, the European Union (EU) is home to 92 million adults over the age of 65 years, but to only 80 million children under 16 years of age[1]. While women (men) in the EU are currently expected to live for 83.6 (78.2) years, their disability free life-expectancy is 19.4 (14.7) years shorter[2]. The increasing burden of age-related functional decline, whether directly linked to non-communicable diseases or not, largely explains this long period of life spent with disability[2].

It is particularly curious that biomedical progress and technological advances over the last decades have failed to change this situation, which was first pinpointed some 40 years ago[3]. Unfortunately, the current health landscape will very soon be considered the "failures of success" suggested by Gruenberg in 1977, with a pandemic of age-related disability[4]. Reducing these excessively long periods of disability is one of the key health and ageing challenges for the years to come.

Following the official endorsement of the second edition of the "International Classification OF Functioning, Disability and Health" (ICF) by all 191 member states of the World Health Organization (WHO) during the 54TH World Health Assembly on 22 May 2001[5], and the 2015 WHO definition of healthy ageing as "the process of developing and maintaining functional ability which enables well-being in older age"[6], this article aims to underscore, yet again, the importance of integrating daily functioning into the clinical practice of all health professionals caring for middle-aged and older adults. The personal life trajectory of these individuals is a unique and complex set of intermingled relations between intrinsic capacity, lifestyles and environment, all of which greatly influence individual functioning.

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The hallmarks and determinants of the ageing process

Ageing is a dynamic, multifactorial and inescapable life course process that ultimately leads to loss of function, crystalizing into a wide range of age-related diseases[7]. The hallmarks of ageing, already well established in animal models[8], include genomic instability, telomere attrition, epigenetic alterations and loss of proteostasis, which are the main culprits of ageing-associated macromolecular damage. Mitochondrial dysfunction, cellular senescence and deregulated nutrient sensing fall into the second category of hallmarks, namely compensatory or antagonistic responses that counterbalance the first set of hallmarks. Finally, altered intercellular communication and stem cell exhaustion are ultimately responsible for the functional decline associated with ageing[9]. However, the ageing rate varies substantially among individuals, even in genetically identical inbred animals[10]. These interconnected mechanisms of ageing, well identified in animal models, strongly suggest that in addition to genetics and time, other factors profoundly modify the ageing process[10].

The heterogeneity of the ageing rate is even more pronounced in humans. Genetics actually has a low impact on the age of death (between 12 and 25%)[11], except in the longest-living families (1 to 10% of a birth cohort)[12,13] who carry variants of the APOE and FOXO3A genes. Moreover, several specific age-related diseases (e.g. diabetes, cardio-vascular events, dementia, osteoporosis) were recently identified as partly genetically based[14]. Beyond genetics and the passage of time, other determinants play a crucial role in the ageing process. These include two types of interacting factors, namely external and personal determinants. External determinants cover factors such as ethnicity, culture, religion, socio-economic and environmental contexts, and also country characteristics, including societal and political choices. In this category, we should also remember to consider security, social inequities and scientific/technological advances. Personal determinants, on the other hand, correspond to the basic and health education, dietary habits, physical activities, life habits and behaviours of the individual. Living and working conditions, as well as lifelong learning, also mediate the ageing process at the individual level.

The loss of physiological reserves

As previously mentioned, the accumulating number of life years lived profoundly changes the physiological reserves, which are essentially constituted during the first period of life. Part of the physiological decline is linked to a reduction in organ reserve (immune, musculo-skeletal and nervous system), which in turn contributes to whole body reserve[15]. The rate of organ decline is estimated to be between 0.5 to 1.4 % per year, and could accelerate beyond the fifth decade of life[16]. This accelerated decline, at first totally silent, explains the progressively increasing vulnerability that becomes evident under stressful conditions (acute disease [e.g. infections] or psychological stress [e.g. divorce, bereavement etc]). All organ functions are affected, but not necessarily to the same extent, which explains that for some individuals, a biologic abnormality is the first alarm, whereas for others, starting to search for words or memory lapses may be predominant. Balance abnormalities, muscular weakness and falls with "advanced age" revelation appears more lately than in the previous generations. A good example affirming that chronological age no longer corresponds to physiological age comes from Japan. The Longitudinal Study on Ageing demonstrated a cohort effect on normal walking speed, whereby the 2006 cohort of men aged between 75 and 79 years had the same normal walking speed (1.29 m/s) as the 1997 cohort of men aged 65-69 years. Similar results were also observed in women (75-79 years in 2006 and 65-69 years in 1997), whose gait speed was 1.24 m/s[17].

Life expectancy in general is on the rise, and functional decline is a manifestation of aging whose onset is insidious, and may therefore be overlooked early in life[18]. However, it starts to become clinically apparent in the fifth or sixth decade of life, and it therefore seems imperative to stress the importance of "midlife" as a useful time to assess the most important proximal risk factors (i.e. close to disease onset), specifically in four closely interconnected domains:

- Integration into society as a whole (education [basic and health], social and health inequities, discrimination, working conditions, pollution [air, noise, toxins, endocrine disruptors], life styles [usual diet, physical exercise, smoking]).
- At the biomedical level: nutritional status [body mass index, waist circumference], cardio-vascular risk score, main biological constants [glycaemia, C reactive protein and Vitamin D] and mental health [anxiety, stress, depressive symptoms, and importantly also cognitive ability [delayed recall and problem solving[19].
- At the functional level, the application of short sarcopenia and frailty questionnaires is always very useful[20]. Moreover, a direct link has been established between walking speed, chair stand, standing balance, grip strength and survival[21].
- Whenever possible, a competence index[22] can also be tested to assess the adoption of new technology and the possible use of a mobile health device to better follow the ageing trajectory and help to manage chronic disease (diabetes or hypertension).

This midlife assessment is important in two regards. Firstly, it may help to identify early functional decline linked to poor nutrition, low physical activity or unhealthy lifestyles and life habits that may be responsible for sarcopenia, frailty, increased risks of fall and other adverse outcomes. Secondly, it can also detect early risk factors of non-communicable diseases (e.g. overweight, obesity, increased blood pressure, depression, or an accumulation of risk factors for cognitive decline).

The importance of these recommendations for midlife

assessment is underscored by the results of the Health and Retirement Study, which included 6,874 community-dwelling adults aged between 50 and 64 years of age (54% men, 80% Caucasians, 15% with low education attendance), in the western part of the United States, who were followed-up for 10 years[23]. The cumulative incidence of impairment in the instrumental activities of daily living (IADLs) at age 64 was 19%, predominantly difficulty shopping for groceries (with 10% affected), managing money (8%) and preparing meals (6%). Most participants who had IADL impairment had impairment in only a single IADL (78%). Surprisingly, impairment was even more frequent in the activities of daily living (ADL), with a cumulative incidence at age 64 reaching 22%, and affecting mainly dressing (14%), whereas difficulties with transferring (11%), toileting (7%), bathing (7%) and eating (3%) were all slightly less frequent. White women, less likely to be married and with a low socio-economic status, were the most disabled, due to chronic clinical conditions (sensory impairment, depression and obesity). In most cases (70%), the impairment was in only one ADL, and recovery to full ADL independence was achieved in 37% at 2 years, and 28% at 10 years of follow up. However, by 10 years, 16% of the population had had one or more episodes of further functional decline, and 19% had died[23].

These interesting results from a 10 year longitudinal study of US community dwelling adults aged between 50 and 64 years deserve to be put in perspective with the findings of a systematic review of 25 studies published from January 1998 to March 2016, aimed at identifying risk factors and protective factors against the development of limitations in ADLs among community-dwelling people aged 75 years and older[24]. Risk factors (identified in at least 2 studies) were higher age, female gender, diabetes, arterial hypertension and stroke. Two protective risk factors emerged from the analysis, namely being married and a high level of physical activity[24]. For several other factors, ambiguous associations were found, such as differences according to age group (50 to 64 and over 75 years), self-reported health score, depression, cognitive abnormalities as measured by the MMSE, and living alone or lower socio-economic status[24]. Although the findings of this systematic review harboured some uncertainty, the compelling need to identify risk factors at midlife is evident, with a view to providing the best medico-social advice, and proposing targeted interventions to delay or prevent the onset not only of chronic diseases, but also of age-related disability.

Non-communicable diseases

Non-communicable diseases develop over long periods of time, and are linked to the cumulative effect of the ageing process itself, and exacerbated by the accumulation of endogenous (pathophysiologic) and exogenous (lifestyle or medication-induced) risk factors[25]. For example, the first signs of atherosclerotic cardiovascular disease (thickening of vessel walls and fatty streaks) can be observed in youth[26], even though clinical events do not occur until midlife or later in life, if at all. This stresses the importance of life-course health promotion (stop smoking, adopt a healthy diet and perform regular physical activity) as well as targeted prevention at midlife (control of dyslipidaemia and hypertension). With the exception of a few positive experiences with such primary prevention campaigns[27], non-communicable diseases are the main cause of mortality and disability not only in developed countries, but also now in the developing world.

Among people aged 60 years and over, the leading causes of death from non-communicable diseases are cardio- and cerebro-vascular disease, cancer, chronic respiratory disease, diabetes mellitus, chronic kidney/liver disease and neurological/mental disorders[28]. Patients suffering from dementia[29] and musculo-skeletal diseases frequently die from a primary cause that is often either infectious (pneumonia) or cardio/cerebrovascular. As mentioned above, the most disabling chronic diseases for the over 60s age group are sensory impairment, back and neck pain, diabetes mellitus, depression, musculo-skeletal disorders and chronic obstructive pulmonary disease (COPD). In those aged over 80, Alzheimer's disease and dementia are major causes of disability[30]. These differences between causes of death and disability are extremely interesting, illustrating that physicians do not pay enough attention to visual, hearing or balance symptoms, as well as painful symptoms (back and neck) pain or depression. This point is far from anecdotal, since many chronic diseases do not occur in isolation, but rather, are associated with other clinical conditions. It is now accepted to speak of co-morbidity when a primary disease exists associated with other pathologies, and of multimorbidity when multiple diseases exist without any primary disease[31]. This concept is important for the patient suffering from chronic disease because it deeply modifies healthcare decisions and delivery. The usual consequence of this accumulation of diseases along the life cycle, often managed by several physicians, is the multiplication of drug prescriptions, resulting in polypharmacy[32]. In patients with polypharmacy, there is increased uncertainty regarding cure, as well as potential for drug interferences and adverse drug reactions[33], which impact the economic cost of disease. Indeed, in patients with multiple chronic conditions, these conditions may interact such that the patient's healthcare costs will be greater than the sum of the costs of the individual diseases[34]. For example, in their study of healthcare expenses for a representative sample of the population covered by the national health insurance, Cortaderona et al reported that the direct costs associated with diabetes in a person without comorbidity were estimated at 1776 €, whereas this metabolic pathology was associated with heart disease, cancer, stroke or renal insufficiency, the costs rose to 2634 €, 2900 €, 3969 € and 8349 € respectively, for a total annual cost of diabetes to the French health insurance system reaching almost 7 billion Euro in 2014[34]. The same

authors also calculated that a preventive strategy to limit the extra costs linked to diabetes could reduce the annual direct costs of diabetes by 15%[34]. This is another strong argument in favor of prevention strategies at midlife and later aimed at delaying onset of disease, and preventing age-related disability.

Comparing the value of medical diagnosis and physical functioning

An original, 6-year, longitudinal study was performed in the Geneva geriatric hospital among 1,951 patients admitted for the first time for an acute medical event[35]. The average age of participants was 84.2 years and the female-male sex ratio was 2.4. Patients systematically had an evaluation of their functional abilities within the 5 first days after admission, using the Functional Independence Measure (FIM)[36,37]. The authors reported a mean number of medical diagnoses of 4.45 per patient, with a maximum of 17 different diagnoses for one patient[35]. The observed life expectancy after hospital discharge was 2.5 years for men and 3.7 years for women. The prognostic value on survival of the ability to perform the FIM at admission and the medical diagnoses at discharge were compared. The results showed that the number of medical diagnoses at hospital discharge explained only 0.5% of death variability; although each new diagnosis increased the death risk by 5%. In contrast, the number of difficulties performing any of the 18 FIM items at hospital admission alone explained up to 14.1% of death variability ($p<0.001$). Thirdly, in this cohort of very old hospitalized patients, the unadjusted global FIM score predicted the death risk 10 times more accurately than the number of medical diagnoses (pseudo $R2 = 0.07$, $p<0.001$)[35]. This large study, unique in its kind, provides crucial insights in the context of the present discussion of functional ability along the lifelong process.

Tackling functional decline from midlife to very old age

As stressed in a recent paper from the European Innovative Partnership of Active Healthy Ageing[38], we should continue to celebrate increases in longevity, but we should nonetheless remain aware that promoting healthy or disability-free life expectancy is now an urgent priority. Implementation of this strategy will call for interventions at different levels across the life process.

• *Promotion of healthy lifestyles*

In a study of 1,810 adults from Stockholm, Sweden who were aged 75 years or older at baseline (October 1987) inclusion in a population-based cohort study, participants were followed up for 18 years, during which time 91.8% of participants died[39]. The authors reported that physical activity was most strongly associated with survival, with those who exercised regularly surviving a median of 2 years longer than those who did not. A prospective study of 3,454 initially disease-free men and women (aged 63.7 ± 8.9 years at baseline) from the English Longitudinal Study of Ageing confirmed the beneficial effects of physical exercise, even when it is taken up relatively late in life[40]. In this study, it was observed that compared to non-physically active individuals, those who engaged in regular moderate or vigorous physical activity, had significantly fewer chronic diseases, less cognitive impairment, less depression, less impairment on ADL/IADLs and less impaired gait speed[40]. In a large French cohort study of 3,005 middle-aged adults (mean age = 51.4 ± 4.3 years) followed up for 12 years in a programme promoting healthy nutrition (increased consumption of fish, fruit & vegetables and micronutrients, low salt) combined with more physical activity, there was a significant increase in self-reported health status, vitality, physical functioning, mental health and social participation[41]. Of note, in this study, it was observed that compliance with dietary guidelines was associated with better future health-related quality of life.

• *Midlife prevention of non-communicable diseases and age-related disability*

Several different types of interventions have been tested in middle-aged adults to modulate the risk of non-communicable diseases later in life. A multicenter randomized trial from Spain, including 5,859 participants (57% women) aged 55 to 80 years at high cardiovascular risk, randomly assigned participants to one of two interventions, namely a Mediterranean diet supplemented with either extra-virgin olive oil, or with nuts. During the 4.8-year follow-up, compared to a control diet (advice to reduce dietary fat), those who had the Mediterranean diet supplemented in virgin olive oil (4 tablespoons a day) or nuts (3 servings per week) had a significantly decreased incidence of major adverse cardiovascular events, with hazard ratios of respectively 0.69 (95%CI, 0.53 to 0.91) and 0.72 (95%CI, 0.54 to 0.95)[42].

The HYVET study randomized 3845 patients with sustained systolic blood pressure of 160 mm Hg or more, and a mean age of 83 years to two groups, name a control group (N=1912) and a treatment group (N=1933) receiving indapamide with additional perindopril if needed to achieve target blood pressure[43]. After a mean of 2.1 years of follow up, there were 431 deaths, and there was a significant reduction in the risk of death from stroke. Also, the risk of all-cause death, any heart failure and any cardiovascular event (cardiovascular death, stroke, myocardial infarction or heart failure) was significantly lower in the treatment group with good blood pressure control compared controls[43]. These findings testify to the considerable prevention of disability in the treated group, and underline that controlling risk factors is beneficial, even in very old[43].

Confirming of the utility of preventive approaches in midlife, a recent Cochrane review including 41 randomized

controlled trials totalling 194,035 participants showed that providing cardiovascular risk scores reduced total cholesterol and systolic blood pressure as compared with usual care[44]. Moreover, providing cardiovascular risk scores may increase preventive medication prescribing (lipid-lowering therapy and antihypertensive drugs) in high-risk groups[44]. It is therefore logical to imagine that better cardiovascular treatment could limit cardiovascular events and their functional consequences.

• *Prevention of hospitalisation related disability*

Adverse events occurring in hospital represent a major public health burden with serious repercussions for the patients. A review of eight studies focusing on the incidence of in-hospital adverse outcomes in 74,485 patients reported a median overall incidence of in-hospital adverse events of 9.2%, with a median percentage of preventability of 43.5%[45]. Temporary disability occurred in a median 19.1% (15.5-30.3%) and permanent disability in 7.0% (6.1-11.0%). In an innovative study from the Netherlands, de Vos et al sought to address the issue of hospital-related disability using program called Pre-Cap (Prevention and reactivation Care program), designed to offer multidisciplinary, integrated and goal-oriented interventions on the physical, social, and psychological domains of functional decline[46]. This includes: 1) early identification of old inpatients at risk, 2) immediate activation of low intensity physical exercise, 3) multidisciplinary geriatric team expertise, 4) support and advice to the informal caregivers, and 5) personal managed care follow up of the patient throughout the entire chain of care[46]. Despite its attractiveness, one year after the implementation of the Pre-Cap program, no difference was found in disability prevention compared to the usual care program[47].

• *Prevention of post-hospitalisation-related disability*

It has been affirmed that early initiation of multiple types of physical activities after hospital admission are effective in reducing the incidence of disability, and favour improved recovery[48].

Conclusion

The analysis of the ageing trajectory clearly demonstrates the constant involvement of functional ability in daily life, from its development in youth, to its preservation through midlife into very old age. While maintaining function appears to be largely related to persistent regular exercise, the risk factors for functional decline are extremely diverse, ranging from a decrease or discontinuation of physical activity, to nutritional/metabolic disturbances, chronic diseases and unfavourable socio-demographic and socio-economic contexts. Prevention of functional decline is a major public health challenge, both for individuals and for society as a whole, and needs to be urgently addressed. Engaging citizens to be conscious of their responsibility for, and role in their own ageing process is equally as important as reinforcing the involvement of society in promoting healthy ageing through enhanced basic and health education, promotion of a healthy diet, long term practice of moderate physical activity, and the continual battle against deleterious life habits and behaviours. The success of these combined actions would be quite simply demonstrated by a change from the current pandemics of morbidity, to the compression of disability, which is expected by all.

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